“COMPARATIVE STUDY OF NEOADJUVANT CHEMOTHERAPY IN HORMONE RECEPTOR POSITIVE AND NEGATIVE LOCALLY ADVANCED BREAST CARCINOMA”

A DISSERTATION SUBMITTED TO THE TAMILNADU
Dr. MGR MEDICAL UNIVERSITY

CHENNAI

In partial fulfilment of the Regulations

for the award of the Degree of

M.S. (GENERAL SURGERY) BRANCH-I

DEPARTMENT OF GENERAL SURGERY
TIRUNELVELI MEDICAL COLLEGE
TIRUNELVELI
MAY 2018

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ACKNOWLEDGEMENT

I am obliged to record my immense gratitude to **Dr.Sithy Athiya Munarvah,** Dean, Tirunelveli Medical College Hospital for providing all the facilities to conduct the study.

I express my deep sense of gratitude and indebtedness to my respected teacher and guide **Dr.M.S.VARADARAJAN,M.S.,** Professor and **Prof.Dr.V.Pandy,M.S.,** HOD, Department of General Surgery, Tirunelveli Medical College, Tirunelveli, whose valuable guidance and constant help have gone a long way in the preparation of this dissertation.

I am also thankful to Assistant Professors **Dr.Sivanupandian,M.S., Dr.Rajkumar,M.S., Dr.Raja,M.S., Dr.Bethsy Priscilla,M.S., and Dr.Irene Aruna Edwin,M.S.,** for their help.

I express my thanks to all Professors, Associate Professors, Assistant Professors, Staff members of the Department of General Surgery and all my Postgraduates colleagues and friends for their help during my study and preparation of this dissertation and also for their co-operation.

I always remember my family members for their everlasting blessings and encouragement.

Lastly, I express my thanks to my patients without whom this study would not have been possible.

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PRINCIPAL INVESTIGATOR: DR.P.S.SONY, MBBS.,

DESIGNATION OF PRINCIPAL INVESTIGATOR POST GRADUATE IN GENERAL SURGERY
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Dear , Dr.P.S.Sony, MBBS., The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on 10.12.15.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1. TIREC Application Form ☐
2. Study Protocol ☐
3. Department Research Committee Approval ☐
4. Patient Information Document and Consent Form in English and Vernacular Language ☐
5. Investigator's Brochure ☐
6. Proposed Methods for Patient Accrual Proposed ☐
7. Curriculum Vitae of the Principal Investigator ☐
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9. Investigator's Agreement with Sponsor ☐
10. Investigator's Undertaking ☐
11. DCGI/DGFT approval ☐
12. Clinical Trial Agreement (CTA) ☐
13. Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA) ☐
14. Clinical Trials Registry-India (CTRI) Registration ☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
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CERTIFICATE - II

This is certify that this dissertation work title **COMPARATIVE STUDY OF NEOADJUVANT CHEMOTHERAPY IN HORMONE RECEPTOR POSITIVE AND NEGATIVE LOCALLY ADVANCED BREAST CARCINOMA** of the candidate **Dr.SONY.P.S,MBBS.,** with registration Number **221511359** for the award of **M.S.** in the branch of **GENERAL SURGERY**. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows **6 percentage** of plagiarism in the dissertation.

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AIMS AND OBJECTIVES
REVIEW OF LITERATURE ANATOMY OF BREAST

INTRODUCTION

Globally, carcinoma breast is one of the commonest malignancies in women and it is the second most common cause of cancer related death in females. In India , it is the second most common cancer, first being carcinoma cervix. According to National Cancer Registry Programme, breast cancer accounts for about > 30% of all cancers in Indian women where urban areas hold the highest incidence.[(1), (2)]

Locally advanced breast carcinoma refers to a diverse and heterogeneous group of breast cancer and represents about 10 – 20% of all breast cancers in the developed world [(3)], while in India this group comprises about 60% of cases.

Globally, definition of Locally Advanced Breast Carcinoma is not uniform in various centres. Recent guidelines of U.S National Comprehensive Cancer Network classified locally advanced breast cancer as AJCC stage III. It includes:

1) Tumour > 5 cms with regional lymph node involvement (N1-N3)
2) Tumours of any size with chest wall or skin involvement or both, regardless of regional lymph node involvement.
3) Presence of regional lymph node involvement irrespective of tumour size
    - Fixed / matted axillary lymph nodes
    - Infraclavicular / supraclavicular lymph nodes

- Internal mammary lymph nodes

(Note: In the 7th edition of AJCC – 2010, ipsilateral supraclavicular lymph node involvement was reclassified as regional lymph node involvement)

Based on probability of getting histologically negative margins after initial surgery, locally advanced breast carcinomas are classified as operable and inoperable. According to NCCN guidelines -2017:

1) Operable LABC : T2N1M0, T3 N0-1 M0
2) Inoperable LABC : Stage IIIA except T3N1M0 , Stage IIIB, Stage IIIC

(Note : NCCN Panel accepts the definition of negative margin as "No ink on the tumour," - 2014 Society of Surgical Oncology-American Society for Radiation Oncology Consensus Guidelines on Margins)

In the past, inflammatory breast carcinoma was considered as a subtype of locally advanced breast carcinoma. [6] On comparison with non-inflammatory forms of locally advanced breast carcinoma, inflammatory breast cancer carries a poor prognosis. So separate guidelines were formed for its management.

Until the middle of last century, primary treatment of LABC was radical mastectomy. This did not change until Stout et al , [4], [5] identified the markers of poor outcome such as skin ulceration, oedema, tumour fixation etc. The Oxford review stated that the use of systemic therapy to

treat micro metastasis, significantly reduces the risk of recurrence and death.

Neoadjuvant therapy, a newer modality of treatment evolved during the last three decades, is being practised all over the world for down staging technically inoperable locally advanced breast cancer prior to surgery. The literal meaning of the term neoadjuvant refers to a “new” (Greek) treatment added to “ assist” (Latin) a primary treatment. The biological rationale for neoadjuvant therapy for breast carcinoma is based on the observation of accelerated metastatic growth following tumour resection in animal models.

This study was conducted in the Department of General surgery , Tirunelveli Medical College to compare the response of neoadjuvant chemotherapy based on hormone receptor status in locally advanced breast carcinoma.

REVIEW OF LITERATURE

ANATOMY OF BREAST

The breasts are a pair of modified sweat glands. It is located in superficial fascia of pectoral region. Breast is covered by skin& nipple-areolar complex .It is composed of fibro-fatty stroma and glandular tissue.

It has a broad base and pointed apex with nipple. It extends from 2nd to 6th rib vertically in midclavicular line and horizontally from lateral margins of sternum to mid-axillary line.

DEVELOPMENT

Ectodermal milk line appears in 7- week embryo on ventral body wall of each side. It extends from limb bud of upper limb to lower limb. Mammary gland arises from the milk line in the pectoral region and others disintegrate.

BASE OF THE BREAST

Base of breast is in contact with pectoral fascia which rests on 3 muscles namely, pectoralis major, serratus anterior superolaterally and inferiorly by aponeurosis of external oblique muscle. Retromammary space is a space filled with loose connective tissue and fat between the pectoral fascia and base.

NIPPLE AND AREOLA

Nipple lies in 4th intercostal space in non-pendulous breast. It is covered with skin which is hairless & thick. It is rich in sensory receptors

and involuntary muscles. Areola is the hyper pigmented rounded area that encircles the nipple. Areola contains sweat and sebaceous glands and involuntary muscles. Montgomery tubercles are enlarged sebaceous glands during pregnancy.

AXILLARY TAILOF SPENCE

Glandular tissue projection from upper- outer quadrant of breast into axilla is the axillary tail of Spence. It passes through foramen of Langer in the axillary fascia. It is in direct contact with anterior group of axillary lymph nodes.

STRUCTURE

Breast consists of breast parenchyma, adipose tissue, connective tissue stroma, lymphatics and blood vessels. Parenchyma of breast is arranged in lobes (15 – 20). Each lobe has a main lactiferous duct. Lactiferous duct receives many smaller ducts. As it converges towards nipple, it gets dilated and form lactiferous sinus and again narrows to reach the summit of nipple and opens. Ligaments of Cooper anchors the gland to overlying skin and base of gland to pectoral fascia.

HISTOLOGICAL TYPE

Breast is a compound tubulo-alveolar gland which is both merocrine and apocrine. Merocrine glands release protein molecules without apical plasma membrane loss whereas apocrine glands release fat globules by loss of plasma membrane.

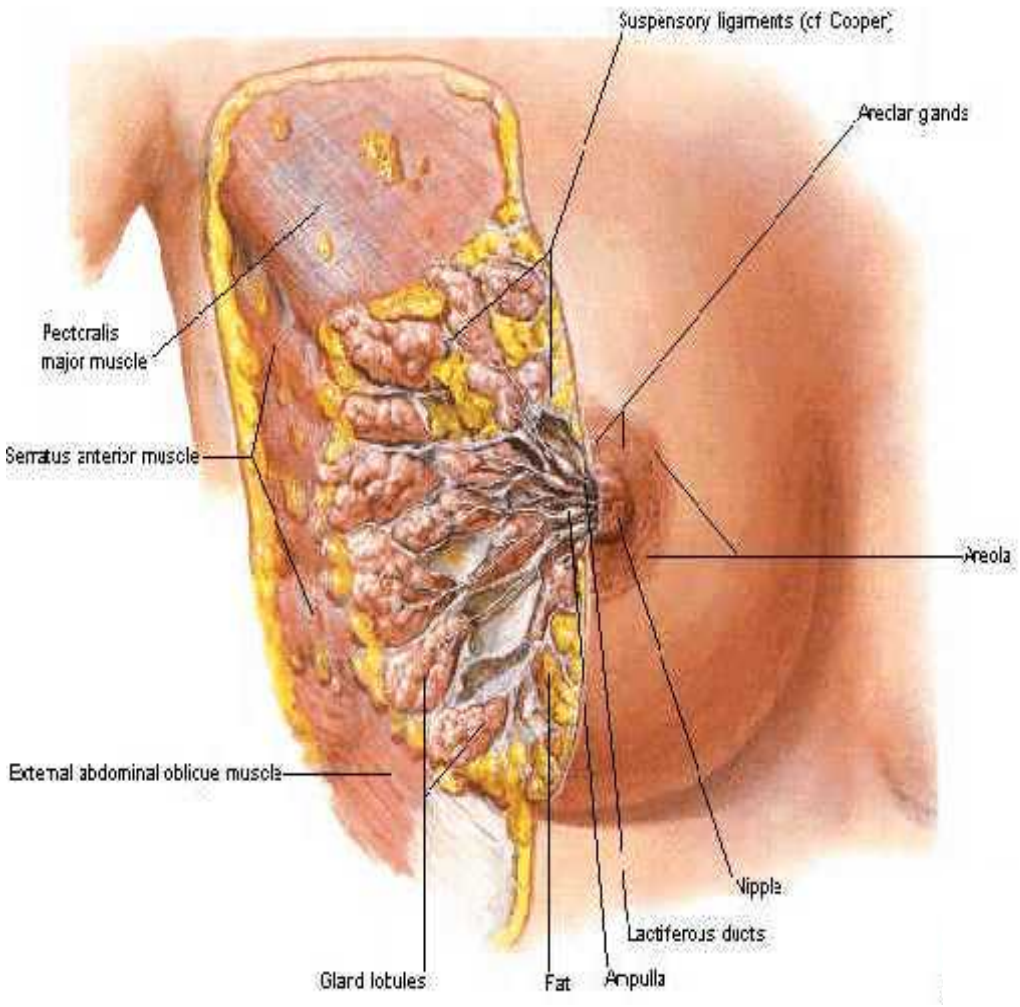


Fig 1

BLOOD SUPPLY

Arterial supply

1) Lateral thoracic artery
2) Perforating cutaneous branches of internal mammary artery
3) Pectoral branches of acromiothoracic and superior thoracic artery
4) Posterior intercostal arteries

Venous drainage

Veins from circular venous plexus of areola drain into axillary, internal thoracic and intercostal veins.

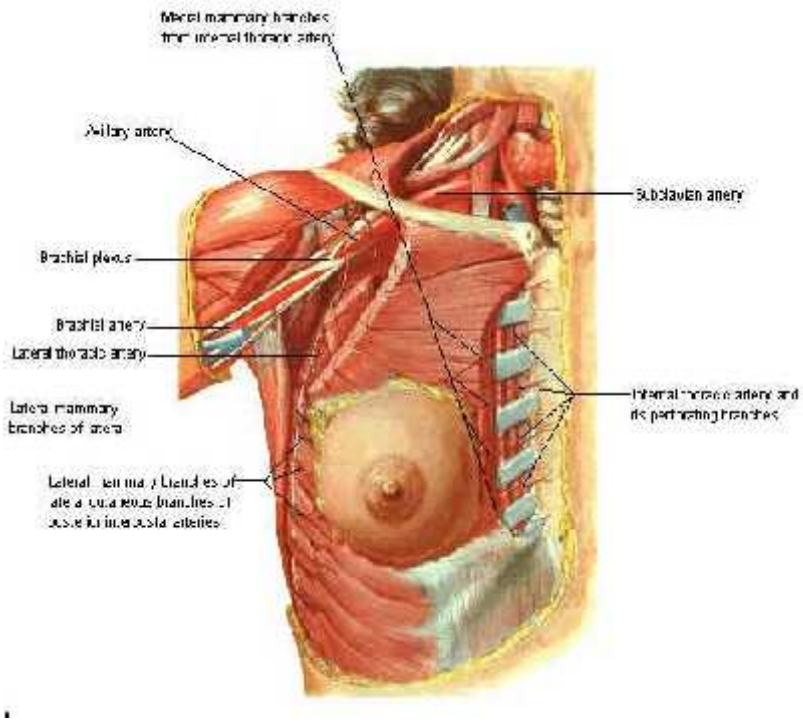


Fig 2- Blood supply

Lymphatic drainage

Breast lymphatics drain by axillary, transpectoral and internal mammary groups of lymph nodes. 75% of lymph flow is to axillary nodes. It consists of 6 groups and are 20 – 40 in number.

1) Anterior or pectoral group
2) Posterior or subscapular group
3) Lateral group

4) Central group

5) Apical group

6) Interpectoral group or Rotter’s node

LEVELS OF LYMPH NODES

Level I : lateral to the pectoralis minor muscle

Level II : posterior to the pectoralis minor muscle

Level III : medial to the pectoralis minor muscle

Lymphatics from the medial part of breast pierces the intercostal muscles and pectoralis major muscle and drains into internal mammary (thoracic) nodes.

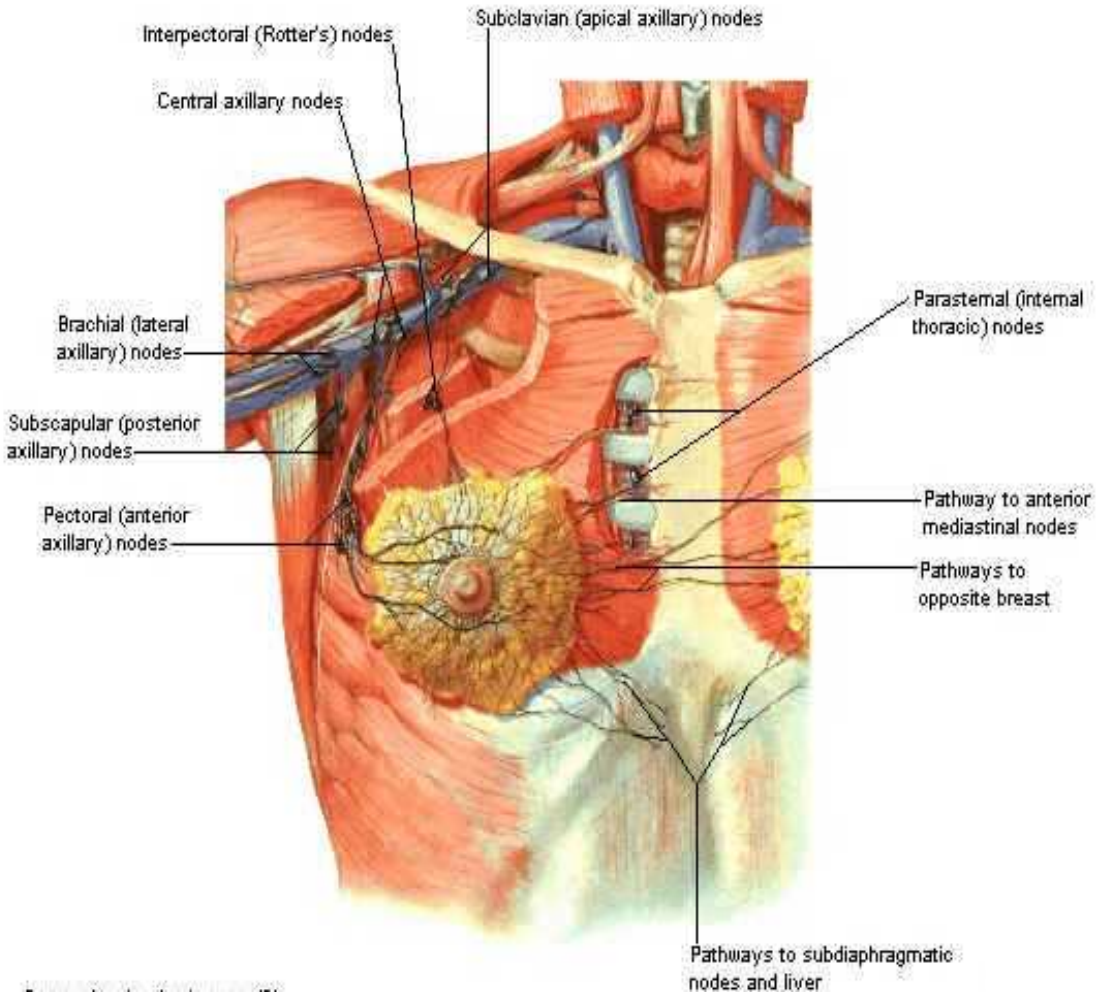


Fig – 3 Lymphatic drainage

EPIDEMIOLOGY OF BREAST CANCER

Breast cancer is the leading cause of cancer deaths in women worldwide , accounting for more than 40,000 deaths annually whereas in developing countries like India, it is the second most common cancer among females. It accounts for about18 % of the cancers in women in India. [7]It is the second most common cause of death in females in

US.[8]Globally each year > 1 million of breast cancer cases are diagnosed. Two out of every 1000 females with age </= 50, will be recently diagnosed to have carcinoma breast & among them about 15 will have the diagnosis of breast cancer at < 50 years of age , thus having a 2 % prevalence of cancer breast.[9]

ICMR has set up six population based cancer registries in India in which Mumbai and Delhi accounts for highest incidence of breast cancer – 32.1/1 lakh.

For breast carcinoma , there exists four components for the hypothesis regarding aetiology . (Adami et al, 98). [10]

1. The incidence of breast cancer depends upon the cell number (Trichopoulos and Lippman, 1992). The supporting evidence for this statement is as follows :

   - Mammographic density express mammary gland mass as a fraction of total breast area , which is a strong predictor of carcinoma breast .

   - Reduced breast carcinoma risk is seen in women having small breast volume, who are motivated for augmentation mammoplasty

2. The determination of response of target cells to hormonal stimulation and their number is done very early in life, even in utero.

   - The evidence to support this hypothesis is given by (Hilakivi-Clarke et al,1997).[11]

- various studies shows a positive correlation between rate of birth &risk of breast cancer (Adami et al, 98).[10]

3. Russo et al[12] concluded that , pregnancy is considered to offer protection [13]against carcinoma breast by terminal differentiation of cells in the mammary gland .

   - Pregnancy increases the risk of breast cancer due to the stimulation of already stimulated cells by the hormones, but in long term it offers a definite protective effect.

4. In the adult life , estrogens and other hormones along with their corresponding receptors, affect the expansion rate of already initiated clones

RISK FACTORS

1) AGE

Age is the most important risk factor. The incidence of breast cancer increases with advancing age in females. Until menopause, it doubles about every ten years[9] . In women less than 20 years , breast cancer is rare and constitutes only 2% of the total. There is an average risk of 12.2% for women being diagnosed with carcinoma breast during their lives at some point.

2) SEX

Breast cancer incidence is more in women than men. Incidence of breast cancer in men is less than 1%.

3) REPRODUCTIVE HISTORY

Nulliparity is a risk factor for carcinoma breast.[14] [24]The breast cancer risk in females with first child birth >30 years of age is twice when compared to females with first child birth in < 20 years of age.[9]First child birth at > 35 years of age carries highest risk. Breast feeding has a protective effect. Induced abortion will not increase the risk. Reproductive risk factors have only mild contribution to the risk of breast carcinoma when compared to other risk factors. (RR 0.5- 2)

4) MENSTRUAL FACTORS

Early menarche (menarche before the age of 12) and late menopause (> 55 years) [9]increases breast carcinoma risk. For each 2- year delay in menarche there is a 10% reduction of risk in carcinoma breast. Early menarche before 12 years of age have approximately 50% higher risk than those with menarche at 15 years of age or later.

Ovarian ablation causing early menopause is associated with a reduction in risk, [32]similarly oopherectomy before 40 years of age is associated with a 40% reduction in risk.

5) FAMILIAL FACTORS

A twofold or threefold increase in the risk is reported in females with a first – degree relative (daughters, mothers and sisters) with breast carcinoma.[9]Risk is even higher approximately 50%, if affected relatives have bilateral carcinoma breast and had early onset. No increase in risk is seen if a distant relative is affected with breast cancer. [20]

6) GENETIC FACTORS

In western countries about 10 % breast cancers are due to genetic factors .[9]Genetic factors like BRCA1 and BRCA2 mutations [21]are associated with increased risk of breast cancer. It is responsible for about 5 – 10% of breast cancer cases.BRCA1 gene is located on chromosome 17 whereas BRCA2 on chromosome 13.BRCA1 and BRCA2 accounts for 40% and 30% of familial breast cancers respectively.[23] But BRCA2 is associated with increased risk of breast cancer in men.

7) PERSONAL HISTORY OF BREAST CANCER

Women with history of breast cancer have a 2 – 4 fold increased risk of developing a second primary cancer in other breast. The risk increases with family history of breast cancer and early age of onset of first primary breast cancer [27] and with history of benign breast disease. [31]

8) HISTOLOGIC RISK FACTORS

Women with previous breast biopsy reports as lobular carcinoma in situ , proliferative changes with atypia and atypical hyperplasia have a higher risk of 5 times than that of general population.[25] [27]

9) ORAL CONTRACEPTIVES

A number of studies suggested increased risk associated with long term use of oral contraceptives in early breast cancer,[26] though it has not been confirmed. The increased risk with recent use reduce within 10 years of cessation of oral contraceptives. Thus the breast cancer risk increases in users of oral contraceptive agents and it decreases as the interval after the cessation of OCP increases.[9] [17]

10) ESTROGEN REPLACEMENT THERAPY

A study in 52,705 women with breast cancer and 108,411 controls from 21 different countries was conducted to assess the relationship of hormone replacement therapy to breast cancer risk. It showed a 2.3% increase in breast cancer risk with HRT per year corresponding to a relative risk of 1.35.[28]

11) SOCIOECONOMIC STATUS

Breast carcinoma is a disease generally recognised as occurring in women with upper socioeconomic status,[29] [30]as measured by either the income or educational status. Studies indicate that these associations reflect the lifestyle changes such as later ages of first child birth.

12) OBESITY

Overweight[22] and high fat diet especially saturated fats increases the risk[18]. In a recent Case- control study , obesity was proven as a risk factor for carcinoma breast in women over 50 years of age who are post menopausal . Vitamin A, micronutrients like Selenium, fruits and vegetables offer protection from breast cancer. [19]

13) ALCOHOL & SMOKING

There are some studies which showed a relation between alcohol intake and breast cancer incidence, but the relation seems to be inconsistent. Similarly smoking has not been proven as an etiological factor for breast cancer.[9] [16]

14) RADIATION increases the risk of breast cancer [9]

PATHOLOGY OF BREAST CANCER

Malignancies of breast are divided into epithelial tumours of cells of lining ducts and lobules and non- epithelial malignancies of supporting stroma

Classification of primary breast cancer

- **Non-invasive epithelial cancers**
  - Lobular carcinoma in situ
  - Ductal carcinoma in situ
    i. Papillary
    ii. Cribriform
    iii. Solid
    iv. Comedo type
- **Invasive epithelial cancers**
  - Invasive lobular carcinoma (10%)

- Invasive ductal carcinoma
    i. Invasive ductal carcinoma NOS
    ii. Tubular carcinoma
    iii. Mucinous or colloid carcinoma
    iv. Medullary carcinoma
    v. Invasive cribriform carcinoma
    vi. Invasive papillary carcinoma
    vii. Adenoid cystic carcinoma
    viii. Metaplastic carcinoma

) Mixed connective and epithelial tumours

- Phyllodes tumour, benign and malignant
- Carcinosarcoma
- Angiosarcoma
- Adenocarcinoma

INVESTIGATIONS

a. FNAC (Fine needle aspiration cytology)

It is a safe, highly accurate, rapid and inexpensive procedure for diagnosing carcinoma in breast masses which are palpable and also in abnormalities of breast which are not palpable detected by mammogram with stereotactic or ultrasound guidance. Sensitivity

and specificity are 90% and 100% respectively. It can be used in evaluation of suspicious second lesion in the same breast of a patient with a known malignancy. It can also be used for the evaluation of suspicious lymph nodes to find out metastatic disease.

Triple Assessment :

Combined use of palpation, mammography and fine needle aspiration has increased the accuracy of diagnosis.

b. Core Needle Biopsy (Trucut biopsy)

It can be performed under ultrasound, mammographic or magnetic resonance imaging guidance.

Sensitivity and specificity are 81 % and 100 % respectively.

Palpable masses : After injection of local anaesthesia, a small skin incision is made and biopsy needle is inserted into the lesion and tissue sample is obtained under vaccum assistance.

Non – palpable lesions : Stereotactic biopsies are taken which includes

1) Suction –assisted core biopsy
2) Automated spring powered core biopsy
3) Advanced breast biopsy instrumentation

c) Excision biopsy

Patients with inconclusive core biopsy results require surgical biopsy for definitive diagnosis. It provides complete surgical removal of tumour. Avoids false negative and insufficient sample.

Non- invasive methods

Detection of small, non palpable breast lesions needs breast imaging techniques. It helps to evaluate clinical findings and guide diagnostic procedures.

1) **X- ray mammography**

It is the primary imaging modality to screen asymptomatic women. Breast is compressed between two plates during mammography to decrease the thickness of tissue through which radiation pass and also to separate adjacent structures thus improving resolution. Two views are obtained in screening mammography- craniocaudal and mediolateral oblique view. For the evaluation of calcifications, magnified views are available.

Breast density limits the sensitivity of mammography. Mammography in younger females less than 30 years of age may produce an image without much definition due to dense breast mass. As age increases, involution of breast tissue occurs and breast is replaced by fatty tissue. Fat absorbs a little radiation on

mammography and provides a contrast background facilitating the detection of smaller lesions.

Present day recommendations suggests mammographic screening for women more than 40 years.

2) **Ultrasonography**

Lesion detected by mammography can be distinguished as solid or cystic by ultrasonography. It can also be used to discriminate lesions in females with dense breasts.

3) **Magnetic Resonance Imaging**

It identifies primary tumour in the breast in females presenting with axillary nodal metastasis without evidence of primary breast carcinoma mammographically. It can also be used to assess the extent of primary breast tumour in young women with dense breast, to evaluate multifocal or multicentric disease, to screen contralateral breast and to evaluate invasive lobular carcinomas.

STAGING OF BREAST CANCER

Staging can be determined clinically before treatment by physical examination and clinical studies , after definite surgical treatment by pathological examination of tumour and lymph nodes.

TNM staging system is used based on size of primary tumour (T), regional lymph node status (N), and presence or absence of distant metastasis (M).

Staging is done to group patients for defining prognosis and to guide treatment recommendations.

TNM Classification for Breast Cancer

Primary tumour (T)

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
Tis (DCIS)	DCIS
Tis (LCIS)	LCIS
Tis (Paget)	Paget disease of the nipple not associated with invasive carcinoma or carcinoma in situ (DCIS and / or LCIS) in underlying breast parenchyma
T1	Tumour $\leq$20 mm in greatest dimension
T1mi	Tumour $\leq$ 1 mm in greatest dimension
T1a	Tumour > 1 mm but $\leq$ 5 mm in greatest dimension

T1b	Tumour > 5 mm but ≤ 10 mm in greatest dimension
T1c	Tumour > 10 mm but ≤ 20 mm in greatest dimension
T2	Tumour > 20 mm but ≤ 50 mm in greatest dimension
T3	Tumour > 50 mm in greatest dimension
T4	Tumour of any size with direct extension to the chest wall and / or to the skin
T4a	Extension to the chest wall, not including only pectoralis muscle adherence or invasion
T4b	Ulceration and / or ipsilateral satellite nodules and / or edema of the skin
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Regional Lymph Nodes

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastasis in ipsilateral axillary lymph node fixed or matted or in clinically apparent ipsilateral internal mammary nodes in the

absence of clinically evident axillary lymph node metastasis

N2a Metastasis in ipsilateral axillary lymph nodes fixed to one another(matted) or to other structures

N2b Metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis

N3 Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement or in clinically apparent ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

N3a Metastasis in ipsilateral infraclavicular lymph node(s)

N3b Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)

N3c Metastasis in ipsilateral supraclavicular lymph node(s)

Distant Metastasis

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

(AJCC Cancer staging manual, 6th ed. New York : Springer 2002, pp. 227-228).

TABLE 1

TNM STAGE GROUPING FOR BREAST CANCER

TNM STAGING OF CARCINOMA BREAST			
0	Tis	N0	M0
I	T1	N0	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

ROLE OF SURGERY IN BREAST CANCER :

Carcinoma breast is the second most common cancer which affects women in India. Surgery was the primary treatment for carcinoma breast for over 100 years. Radical mastectomy was the single most effective treatment modality for cure. It was the most commonly recommended surgical procedure until the last 2 decades.

Pre-Halstedian Era:

The unfortunate victim of carcinoma breast in the Pre Halstedian era would suffer from malodorous, uncontrolled and fungating disease with or without excruciating pain. The five year survival after the diagnosis of breast cancer ranged from 11-18%.

The Halstedian Era :

The approach to carcinoma breast was revolutionized by the description of hypothesis of Halsted Handly based on Virchow's pathology. It postulated the growth of tumours within the organ followed by invasion into lymph nodes by either permeation or embolisation, subsequently by a third step of distant metastasis. It was logical to subject the patients with carcinoma breast to enbloc excision of tumour bearing organ along with its lymphatic drainage. Lewis and Rinehoff study results from John Hopkins University found that only 36% survival was reported

at 5 years and 12% at 10 years . Widespread acceptance of this treatment is attributed to the remarkable success in decreasing the incidence of local disease and thus improvement in quality of life.

The Deterministic Era

This era was marked by two important events - one was the contribution to the biological model by Fischer and the second one was the application of possible benefit of early detection of cancer breast.

Fisher's postulate was that occult micro metastasis existed before the diagnosis of clinically evident carcinoma breast itself. Hence this model justified the systemic therapy usage to suppress or eradicate micro metastasis. There are so many datas on adjuvant systemic therapy which shows moderate gain in overall survival and disease free interval.

Radical Mastectomy:

It is the enbloc removal of the breast, axillary lymph nodes, pectoralis major and pectoralis minor muscles. It includes level III axillary lymph node dissection and removes the Rotter's node thus resulting in conspicuous deformity of chest. Radical mastectomy is reserved for locally advanced breast carcinoma cases which require removal of pectoralis major muscle and an axillary dissection to achieve adequate surgical margin.

Modified Radical Mastectomy :

Modified radical mastectomy procedure was first introduced by Patey and Dyson. In Patey's modified radical mastectomy procedure , pectoralis minor is removed and axillary dissection is done completely. The second type of modified radical mastectomy was described by Auchincloss in which pectoralis minor muscle is preserved and dissection of the apex of the axilla was accompanied by gentle retraction of pectoralis minor . In 1958, John Madden of Newyork preserved both pectoralis major and pectoralis minor, lateral and medial pectoral nerves while doing modified radical mastectomy.

Breast Conservation Therapy (BCT) :

The principles which led to modified radical mastectomy also contributed the development of breast conservation therapy , following some prospective randomized trials in 1970s.

MRM Vs BCS + RT (Breast conservation surgery + radiotherapy) showed equal long term survival. The local recurrence rate at 10 years for BCS + RT is 4 -20% while for MRM it is 2 - 9%.

MANAGEMENT OF THE AXILLA :

In patients with invasive carcinoma breast , complete dissection of axilla was considered to be the standard management for years. According to halstedian concept, axillary dissection was thought to be a major component on surgical cure for carcinoma breast . In that concept, nodes in the axilla were considered as the filter before the cancer cells spreads to distant sites.

In addition to the potential survival benefit, axillary dissection is also considered to be useful in assuring local tumour control in axilla and assessing prognosis.

By 1970 , there were evidences that dissection of axilla had a limited impact on overall survival . This was strongly demonstrated in NSABP trial B-04. In NSABP trial, patients with negative axillary nodes clinically were subjected to radical mastectomy along with observation or dissection of lymph nodes in axilla and a delayed dissection was done if node appeared positive and radiotherapy was given to the regional lymph node basins. By doing so there were no statistical difference in the 10 year survival rate was found among these groups. A number of studies were carried out to determine the extend of lymph node dissection in axilla in order to achieve a complete cure of axilla. Many of these studies focussed on the likelihood of skip metastasis ie. involvement of upper axillary

lymph nodes (level III) in the absence of involvement in the lower nodes (level II).

Involvement of level III lymph nodes are rare when both level I and II lymph nodes are negative. Most authors concluded that level I dissection provides a very accurate staging information whereas majority have agreed that removal of both level I and II lymph nodes are required. Level III dissection of axillary lymph nodes increases the morbidity. It provides only a little additional prognostic information. The chance of local recurrences of carcinoma breast is related to the number of lymph nodes removed, when patients undergo limited axillary dissection procedures. The five year recurrence rate is about 20% when no lymph nodes are removed whereas it is only 10% when only one or two negative nodes are removed. The number of involved axillary lymph nodes remains the single most important factor of prognosis.

SENTINEL LYMPH NODE BIOPSY :

Sentinel lymph node is the 1st lymph node which receives the lymphatic drainage from the tumour. Sentinel lymph node dissection helps in reducing the morbidity caused by surgery of axilla. It provides accurate information about staging of carcinoma. Patients with clinically negative axillary nodes can be subjected to sentinel lymph node dissection and if it is positive, these patients can undergo complete axillary lymph node

dissection. The surgeon identifies the first draining (sentinel) lymph node by injecting blue dye or radioactive colloid or both around the primary tumour. This passes through the lymphatics and accumulates in the first draining node. The sentinel lymph node is detected by gamma probe, and is identified as a radioactive node, blue node or both . It is removed and sent for histopathological evaluation. Sentinel lymph nodes are evaluated by multiple H&E staining for cytokeratin. Axillary dissection can be avoided in patients with no metastatic involvement of sentinel lymph node. A critical study about evaluation of sentinel lymph node dissection was the NSABP – 32 trial.

Absolute Contraindications :

1. Palpable axillary lymph node metastasis
2. Multifocal breast cancer.
3. Prior breast / axillary surgery (might interfere with lymphatic drainage)

(Jatoi Ismail, Surgical clinic N. America Oct 1999).

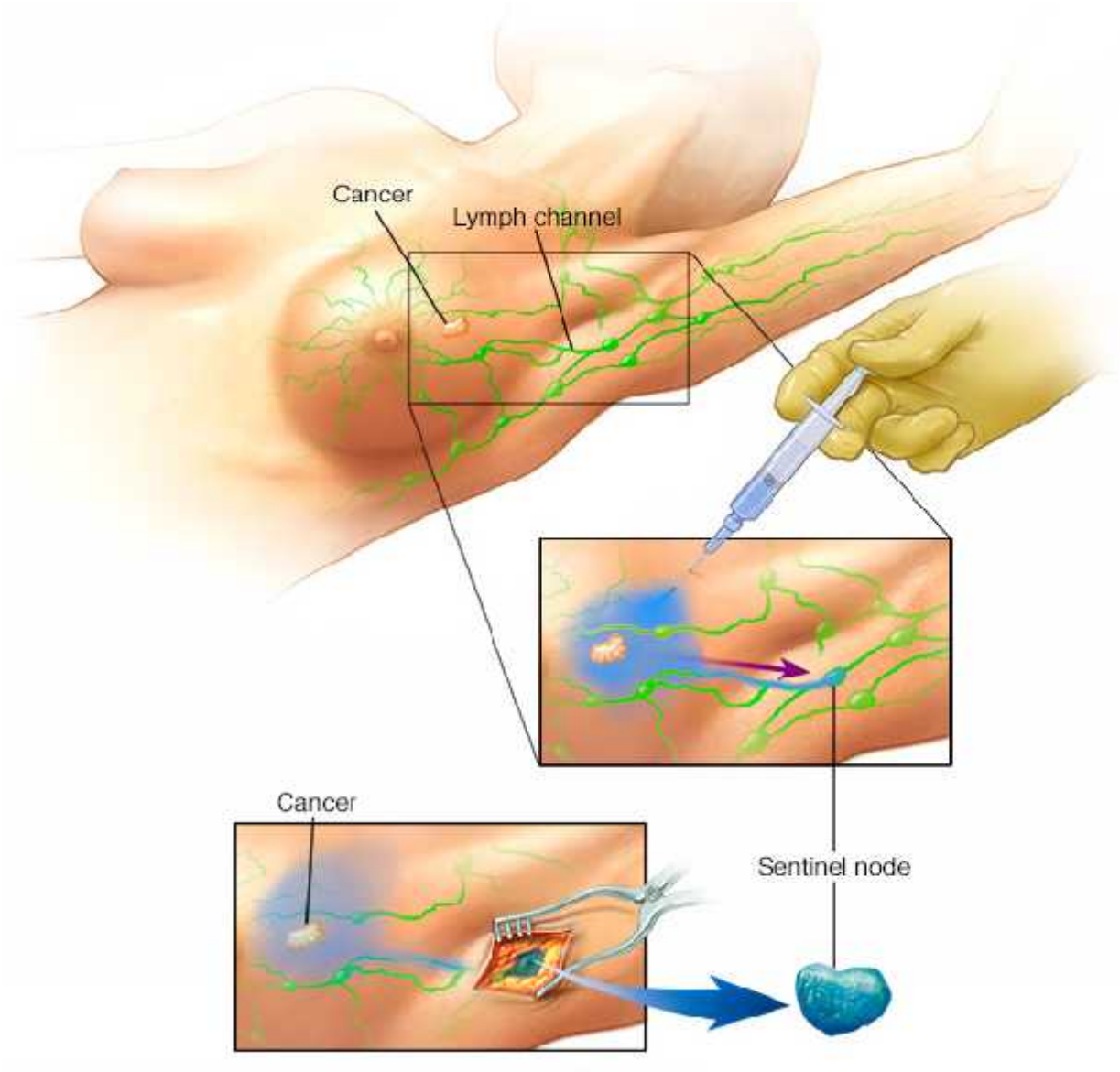


Fig 4 – Sentinel lymph node biopsy

ROLE OF SYSTEMIC THERAPY:

The current biological concept is that the first cell of the carcinoma breast itself is metastatic disease and so the occult or micro metastasis is present even at the time of clinically evident breast carcinoma. Hence for the long term improvement, breast cancer patients need a systemic control of their disease which is not provided by either surgery or radiotherapy. So

several chemotherapy trials have been conducted in response to the concept of “Carcinoma Breast is a systemic disease hence should be treated systemically”. These systemic therapies aim at treating and preventing recurrence of breast cancer which are metastatic.

Patients with carcinomas which are node positive are benefited by chemotherapy irrespective of the hormone receptor status. Systemic therapy includes chemotherapy and hormone therapy .

The various chemotherapeutic regimes are as follows:

CMF : Cyclophosphomide, Methotrexate, 5 -Flurouracil

FAC : 5-Flurouracil, Adriamycin, Cyclophosphomide.

CEF : Cyclophosphomide, Epirubicin, 5- FU

AC : Adriamycin, Cyclophosphomide

EC : Epirubicin , Cyclophosphamide

<u>Newer Chemotherapeutic Agents</u> :

Taxanes: Paclitaxel, Docetaxel, Gemcitabine, Vinorelbine

The biological parameters in terms of ER and PR receptor, DNA ploidy , oncogenes such as HER-2/neu , S phase fraction , proliferation indices – Ki 67 and others are certain indicators to decide the choice of the drug and the regime.

Timing of Systemic Therapy :

Systemic therapy was considered to be the adjuvant treatment being given after the surgery or radiation. But in recent years there has been significant changes in the rationale of using systemic therapies. This gave rise to the concept of neoadjuvant chemotherapy. The tumours which are amenable to surgery are given adjuvant systemic therapies whereas preoperative systemic therapies are tried in patients with inoperable breast cancers at the time of presentation.

CHEMOTHERAPEUTIC REGIMENS :

CMF chemotherapy

- Cyclophosphamide given 100 mg/m^2 per oral for days 1- 14
- Methotrexate is given 40 mg/m^2 as IV on days 1 & 8
- 5- Fluorouracil given 600 mg/m^2 as IV on days 1 & 8

These drugs are cycled every 28 days x 6 cycles

FAC chemotherapy

- Cyclophosphamide = 100 mg/m^2 Per oral on days 1 – 14
- Adriamycin = 60 mg/m^2 as IV on days 1 & 8
- 5 – Fluorouracil = 600 mg/m^2 as IV on days 1 & 8

Cycled every 28 days x 6 cycles

Dose dense AC chemotherapy

- Doxorubicin = 60 mg/m^2 as IV on day 1
- Cyclophosphamide = 600 mg/m^2 as IV on day 1

Cycled every 14 days x 4 cycles

AC chemotherapy

- Doxorubicin = 60 mg/m^2 as IV on day 1
- Cyclophosphamide = 600 mg/m^2 as IV on day 1

Cycled every 21 days x 4 cycles

TAC chemotherapy

- Docetaxel = 75 mg/m^2 as IV on day1
- Doxorubicin = 60 mg/m^2 as IV on day 1
- Cyclophosphamide = 500 mg/m^2 as IV on day 1

Cycled every 21 days x 6 cycles

EC chemotherapy

- Epirubicin = 100 mg/m^2 as IV on day 1
- Cyclophosphamide = 830 mg/m^2 as IV on day 1

Cycled every 21 days x 8 cycles

AC followed by docetaxel chemotherapy

- Doxorubicin = 60 mg/m^2 as IV on day 1
- Cyclophosphamide = 600 mg/m^2 as IV on day 1

  Cycled every 21 days x 4 cycles
- Docetaxel = 100 mg/m^2 as IV on day 1 - cycled every 21 days x 4 cycles

Toxicities of systemic chemotherapy

Very common (>25%)

- Alopecia
- Amenorrhea
- Hot flushes

Common(<25%)

- Oedema
- Leukopenia
- Musculo skeletal pain
- Nausea

Uncommon(<10%) :

- Leukopenic fever
- Stomatitis

- Thrombophlebits
- Weight gain

Cardiac toxicity : Since 1980s , anthracycline based regimes with adriamycin or epirubicin was used in treatment of breast cancer. According to Azim et al [41] , these drugs has a significant dose dependent cardiac toxicity risk. There is a 5 % chance of congestive cardiac failure .[42] This is believed to be due to damage of myocardial cells by free radicals generated on administration of anthracyclines.[41]. The risk factors are hypertension , previous history of coronary artery disease, old age and previous radiotherapy.

Secondary cancers : Carcinoma breast patients who received chemotherapy has a greater risk of developing a secondary cancer [41] ie . leukemia or myelodysplastic syndrome [43- 45]. But in clinical practise , leukemia risk is very low if the anthracycline or cyclophosphamide dose used are not exceeding the cumulative dose.

Neurotoxicity and cognitive functions: Cognitive impairment following chemotherapy is seen in 20 – 30 % of treated patients even though its incidence remains unclear. Ahler et al [47] , stated that carcinoma breast patients treated with chemotherapy has reduced psychomotor functioning

and memory. But there are no proven methods for treatment or prevention of chemotherapy associated cognitive impairment. There were several trials on modafenil and erythropoietin in treating cognitive impairment but it failed to show a convincing improvement in symptoms. [48],[49],[50]

Premature menopause : Chemotherapy induces menopause either permanent or temporary [51]. The risk of developing chemotherapy induced amenorrhoea is dependent on age of the patient, chemotherapy drug and number of cycles of chemotherapy administered.[52] CAF regimen induces menopause in 23-47 % patients with < 30 years of age and 80- 89 % of patients with > 40 years .[53],[54]

Targeted Therapy :

Trastuzumab (herceptin) is a humanized recombinant IgG1 monoclonal antibody, approved in 1998, against HER2/neu used both as single agent and in combination chemotherapy. It is found to be effective even though the cost is high.

Transtuzumab based chemotherapy regime :

- FEC chemotherapy followed by Pertuzumab or Transtuzumab & Paclitaxel

- Pertuzumab or Transtuzumab & Docetaxel followed by FEC chemotherapy
- Pertuzumab or Transtuzumab & Docetaxel followed by FEC chemotherapy

Side effects : cardiac failure, LV dysfunction(risk factors are older age group, prior cardiac disease etc)

Hormone Therapy : Given in ER/PR positive cases.

Predictors of Hormone therapy are

1. Patients with prolonged disease free interval after primary treatment
2. Metastasis to soft tissue, bone and lungs
3. Elderly patients, perimenopausal, post menopausal responds better.

Hormones are :

1. **Tamoxifen and its analogues**: Toremifene, Droloxifene, Idoxifene
2. **Targeted antioestrogen**

Raloxifene – is selective oestrogen receptor modulator (SERM).

3. **Aromatase Inhibitors** :

- Non-steroidal – Anastrozole , Letrazole, Fadrazole,
- Steriodal – Exemestene, Formestene

4. **LHRH Agonists** :

Produces chemical or medical oophorectomy – Buserlin, Goserlin

TAMOXIFEN

It is an anti-oestrogen which blocks oestrogenic stimulation of breast cancer cells. In ER positive breast carcinomas, tamoxifen decreases the annual recurrence by 39 % and deaths by 31 % irrespective of age, menopausal status, axillary lymph node status and use of chemotherapy. In the set of patients receiving tamoxifen and chemotherapy, chemotherapy should be offered first followed by tamoxifen. Randomized trials have stated that tamoxifen use for 5 years give better responses.

Side Effects :

- Fatigue
- Nausea
- Hot flushes
- Endometrial carcinoma

NEOADJUVANT CHEMOTHERAPY :

Neoadjuvant chemotherapy denotes the use of chemotherapy as the initial treatment for patients before surgery. Neoadjuvant chemotherapy is being advocated in the treatment of a variety of neoplasms.

- Breast carcinoma
- Anorectal carcinoma
- Bladder carcinoma
- Laryngeal cancer
- Osteogenic sarcoma
- Soft tissue sarcoma

PRINCIPLES OF NEOADJUVANT CHEMOTHERAPY :

Benefits of preoperative chemotherapy

- It facilitates conservation of breast
- It renders inoperable tumours operable
- It provides an important prognostic information on response to therapy, especially in triple negative breast carcinomas and HER2- positive breast carcinomas , at an individual level
- It gives time for genetic testing
- It gives ample time to plan the reconstruction of breast in patients undergoing mastectomy

Opportunities ;

- It may allow sentinel lymph node biopsy alone if an axilla which is positive is cleared with therapy
- It provides an opportunity to change systemic treatment if there is no response to preoperative therapy or if the disease progress
- It may allow the addition of other adjuvant treatments in patients who responds poor to preoperative treatment
- It may allow less radiotherapy to axilla if the axillary nodal disease is cleared
- It provides an excellent research platform for testing novel therapies

Cautions :

- Possibility of overtreatment with systemic therapy due to overestimation of clinical stage
- Possibility of under treatment of loco-regional tumour burden with radiotherapy due to underestimation of clinical stage
- Possibility of progression of disease during preoperative chemotherapy

Candidates for neoadjuvant therapy :

- Patients with inoperable carcinoma breast
- Inflammatory breast cancer

- Bulky or matted axillary lymph nodes
- N3 nodal disease
- T4 tumours
- Patients with operable carcinoma breast having a large primary tumour relative to the breast size (who desires breast conservation)

Non- candidates for neoadjuvant chemotherapy

- Patients who have extensive in-situ disease and when the extent of invasive carcinoma is not well defined
- Patients who have a poorly delineated tumour preoperatively
- Patients with non – palpable and non- clinically assessable tumour

NEOADJUVANT CHEMOTHERAPY REGIMENS :

Regimens for HER2 – negative carcinoma breast

- Dose- dense AC = (Doxorubicin & Cyclophosphamide) followed by Paclitaxel every 2 weeks
- Dose- dense AC = (Doxorubicin & Cyclophosphamide) followed by weekly Paclitaxel
- TC (Docetaxel and Cyclophosphamide)
- Dose- dense AC = (Doxorubicin & Cyclophosphamide)

- AC = (Doxorubicin & Cyclophosphamide) every 3 weeks
- CMF = (Cyclophosphamide , Methotrexate & 5-Fluorouracil)
- FAC = (5- Fluorouracil , Adriamycin & Cyclophosphamide)
- AC followed by Docetaxel every 3 weeks
- AC followed by weekly Paclitaxel
- EC - Epirubicin & Cyclophosphamide
- TAC - Docetaxel & Doxorubicin & Cyclophosphamide

Regimens for HER2- positive carcinoma breast

- AC followed by Transtuzumab or Pertuzumab
- TCH (Docetaxel , Carboplatin & Transtuzumab or Pertuzumab)
- AC followed by Docetaxel , Transtuzumab or Pertuzumab
- Docetaxel , Cyclophosphamide & Transtuzumab
- FEC followed by Docetaxel & Transtuzumab or Pertuzumab
- FEC followed by Paclitaxel & Transtuzumab or Pertuzumab
- Paclitaxel and Transtuzumab
- Pertuzumab or Transtuzumab and Docetaxel followed by FEC
- Pertuzumab or Transtuzumab and Paclitaxel followed by FEC

HORMONE RECEPTORS

Hormone has a very important role in progression and development of carcinoma breast, for example estrogen and progesterone . The risk of breast cancer is proportional to estrogen exposure. Hormone receptor positive breast cancer patients even after diagnosed to have metastatic disease survive 2 – 3 times longer than hormone receptor negative carcinoma patients. Patient with tumours positive for hormone receptors are candidates for hormone therapy.

Determination of steroid hormone receptors

Methods : 1) Multipoint titration

2) Analyses of sucrose gradient

Titration procedure was the most commonly used method. It uses charcoal coated with dextran to remove the steroid that is unbound from intracellular receptors. [2]

Now this is by immunohistochemical analysis .

Response to chemotherapy

James et al [55]reported that absence of steroid hormone receptors will result in loss of the differentiated functions and it correlates with rapidity in growth rate of tumours. Hence , this rapidly growing carcinomas which are hormone receptor negative will respond to chemotherapy better than

hormone receptor positive tumours. Knight et al [56]concluded that patients with ER positive breast cancers have a longer disease free survival period on comparison with those having hormone receptor negative cancers, irrespective of their axillary nodal status and menopausal status. They reported that increase incidence of ER negative cancers in premenopausal patients are associated with increased sensitivity to chemotherapy.

NSABP conducted many randomized trials on chemotherapy in operable cancer breast patients and reported that the response of this was more in premenopausal age group.

Lippman et al [57] determined the correlation between increased growth rate of carcinoma breast and chemotherapy response.

ESTROGEN and PROGESTERONE receptors

Steroid hormones usually bind with high affinity and specificity to intracellular receptors. Steriod receptors such as Oestrogen and Progesterone receptors are located in cell nucleus. Many of the genes which are regulated by the steroid receptors involve in cell growth regulation and it is now believed that these are very relevant on the treatment and behaviour of breast cancer. Oestrogen receptor is of very importance in cancer breast , as a cause of growth and as a therapeutic agent to inhibit the growth in the breast cells . Oestrogen receptor is a nuclear steroid receptor . It can be measured by several methods, the older

method being ligand binding, then came the immunoassay method and now the immunocytochemistry. (It can be performed on routine histologic sections of tumour) .

OESTROGEN RECEPTOR

Oestrogen receptor was first identified in the 1960s.Subsequent studies have proved that ER is very important in the carcinogenic process. Its inhibition, by endocrine targeting - oopherectomy or by oestrogen agonists (selective oestrogen receptor modulators) or by blocking conversion of androgens to estrogens, forms the mainstay of endocrine therapy for carcinoma breast . Therefore the oestrogen receptor status has been used since 1970s in the management of breast cancer , as a prognostic factor for early recurrence and as an indicator of endocrine responsiveness.

Majority of carcinoma breast cases about 75 % are oestrogen receptor positive .In women older than 50 years of age , about 80 % of tumours are oestrogen receptor positive whereas there is a decline in the rate of oestrogen receptor positivity in tumours of breast in women of age less than 50 years , that is about 65 % . More than 90% of cases show oestrogen receptor positivity in tumour types such as cribriform, tubular , lobular and mucinous. Even though oestrogen receptor positive tumours are of low grade, associated with better outcome, show less aggressive

characteristics, long term survival rate is similar for both ER positive and ER negative tumours, indicating that ER has lost its importance as a prognostic factor .Though oestrogen receptor has lost its value as a prognostic factor, there is a very big advantage in determining the ER status of a tumour so that we are able to find that whether the tumour responds to endocrine therapy or not . Till now it is believed that ER is a major determining factor in the treatment of carcinoma breast.

PROGESTERONE RECEPTOR

Progesterone receptor is an oestrogen regulated gene. So its expression denotes the functioning of oestrogen pathway. About 55 – 65 % of tumours are progesterone receptor positive . PR positive tumours have a better outcome than PR negative tumours.

AIMS AND OBJECTIVES

1) To assess the clinical response & pathological response of neoadjuvant chemotherapy in locally advanced breast carcinoma.
2) To compare the response of neoadjuvant chemotherapy in hormone receptor positive and hormone receptor negative locally advanced breast tumours.
3) To assess the feasibility of surgery in inoperable locally advanced breast carcinoma after neoadjuvant chemotherapy.

MATERIALS AND METHODS

Type of study **:** Prospective study

Setting:

The study was conducted in the Department of General Surgery, Medical College Hospital, Tirunelveli during the period from January 2016 to March 2017

Materials and Methods:

A prospective study was done to evaluate the response of neoadjuvant chemotherapy in locally advanced breast carcinoma in clinical and pathological terms. 50 cases of LABC were included in the study after ruling out metastasis .

All these cases were given CAF regimen – 3 cycles and were assessed for the response.

CAF regimen- dose :

Cyclophosphamide - 500 mg/m^2

5- Fluorouracil - 500 mg/m^2

Adriamycin - 50 mg/m^2

ASSESSMENT OF CLINICAL RESPONSE

The clinical response was assessed by the **RECIST** criteria

Tumour lesions were measured in the plane of longest diameter.

Tumours were termed measurable if the minimum size along longest diameter is

- 10 mm by CT scan (slice thickness not greater than 5 mm)
- 10 mm by caliper measurement
- 20 mm by chest x-ray

Evaluation of target lesions – Clinical Response

1) Complete Response (CR)

Disappearance of all target lesions.

2) Partial Response (PR)

At least a 30 % decrease in the sum of diameters of target lesions.

3) Progressive Disease (PD)

At least a 20% increase in the sum of diameters of target lesions.

4) Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Surgical treatment

Following neoadjuvant chemotherapy, operable locally advanced breast cancer patients underwent surgery (modified radical mastectomy). The specimen was subjected to histo-pathological examination and assessed for pathological response.

Pathological Response

1) **Complete Response**

Clearance of invasive tumour in breast and axilla.

2) **Partial Response**

Persistence of less than 10 microscopic foci of invasive tumour cells in the breast or in the axilla.

3) **No response**

Residual tumour in the resected specimen.

Inclusion criteria:

- Patients with locally advanced breast carcinoma who received neoadjuvant chemotherapy and underwent surgery.

Exclusion criteria:

- Neoplasms of breast other than locally advanced breast carcinoma
- Inflammatory carcinoma of breast
- Tumours with HER-2 neu receptor positivity

Statistical Analysis

In this study, continuous variables are summarised as arithmetic mean. The Chi- square test was applied to compare the attributes in Neoadjuvant Chemotherapy results. All the tests were conducted by assuming that the level of significance was fixed as $\alpha = 0.05$ and all the tests were two sided. The statistical analysis were carried out using Sigma Plot from SYSTAT Software Package, USA.

RESULTS

In this prospective study, 50 patients were chosen from the outpatient wing of Department of General Surgery, Tirunelveli Medical College Hospital during the period between January 2016 – March 2017.

The mean age of my study population was 47 years and mean tumour size was 8 cms. Patients with tumour at stages T2, T3 and T4 represented 2%, 42% and 56% respectively. Nodal stage is as follows – N0- 2%, N1- 80%, N2- 16 and N3- 2% Thus patients in clinical stages III A, III B, III C were 44% , 54 % and 2 % respectively.

In the study conducted by Alvarado Miranda et al, mean age of the study population was 50 years and mean tumour size was 3.9 cms.In that study , !9.6%, 44.6% and 35.7% patients had T2, T3 and T4 stages respectively. 49.1%, 50% and 0.9% patients had N1, N2 and N3 nodal stages respectively

TABLE 2

BASELINE PATIENT CHARECTERISTICS

		My study	Study by Alvarado Miranda et al,
Mean Age (years)		47	50
Mean tumour size (cms)		8	3.93
Clinical T stage	T2	1 (2%)	22 (19.6%)
	T3	21(42%)	50(44.6%)
	T4	28(56%)	40(35.7%)
Clinical N stage	N0	1(2%)	-
	N1	40(80%)	55 (49.1%)
	N2	8(16%)	56 (50%)
	N3	1(2%)	1(0.9%)
Clinical stage	II B	-	24(21.4%)
	III A	22(44%)	48(42.9%)
	III B	27(54%)	40 (35.7%)
	III C	1(2%)	-

TABLE 3 - AGE GROUPS OF THE PATIENTS

S.No	Age	Total no. of cases, n= 5	Percentage
1	</= 40	10	20
2	41 – 50 years	22	44
3	51 – 60 years	17	34
4	>60 years	1	2

44 % of patients fall between 41 – 50 years of age and the youngest patient was 31 years old.

CHART 1- AGE DISTRIBUTION OF PATIENTS

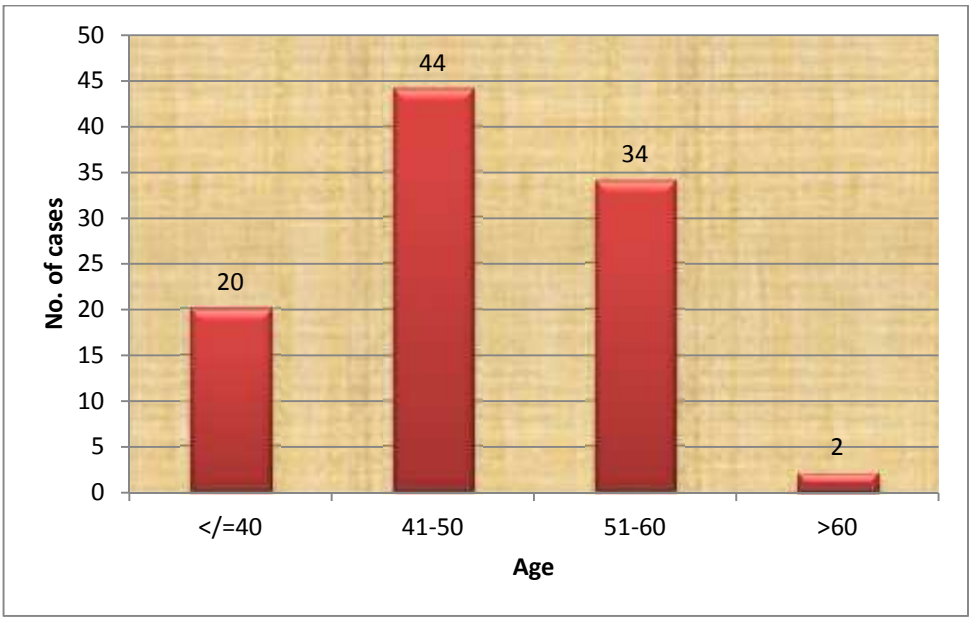


TABLE 4 - SITE OF TUMOUR

Site of tumour (Quadrant)	No. of patients,n=50	Percentage	Marshall and Higginbotham Statistics
Upper outer	31	62	60
Upper inner	7	14	12
Lower outer	5	10	10
Lower inner	3	6	6
Central	4	8	12

Upper outer quadrant was the commonest site of tumour in my study (62%)

CHART 2- SITE OF TUMOUR

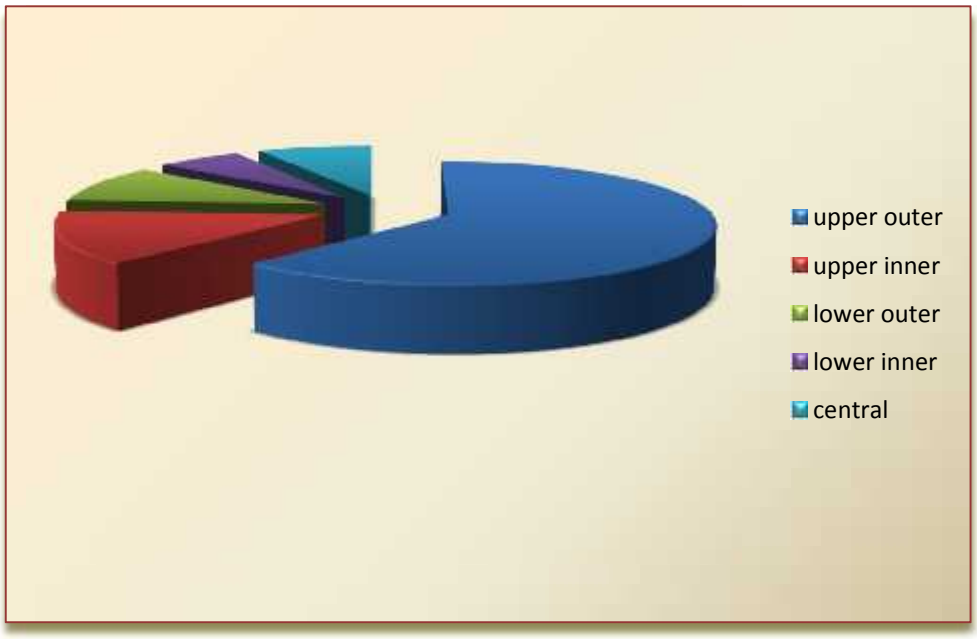


CHART 3

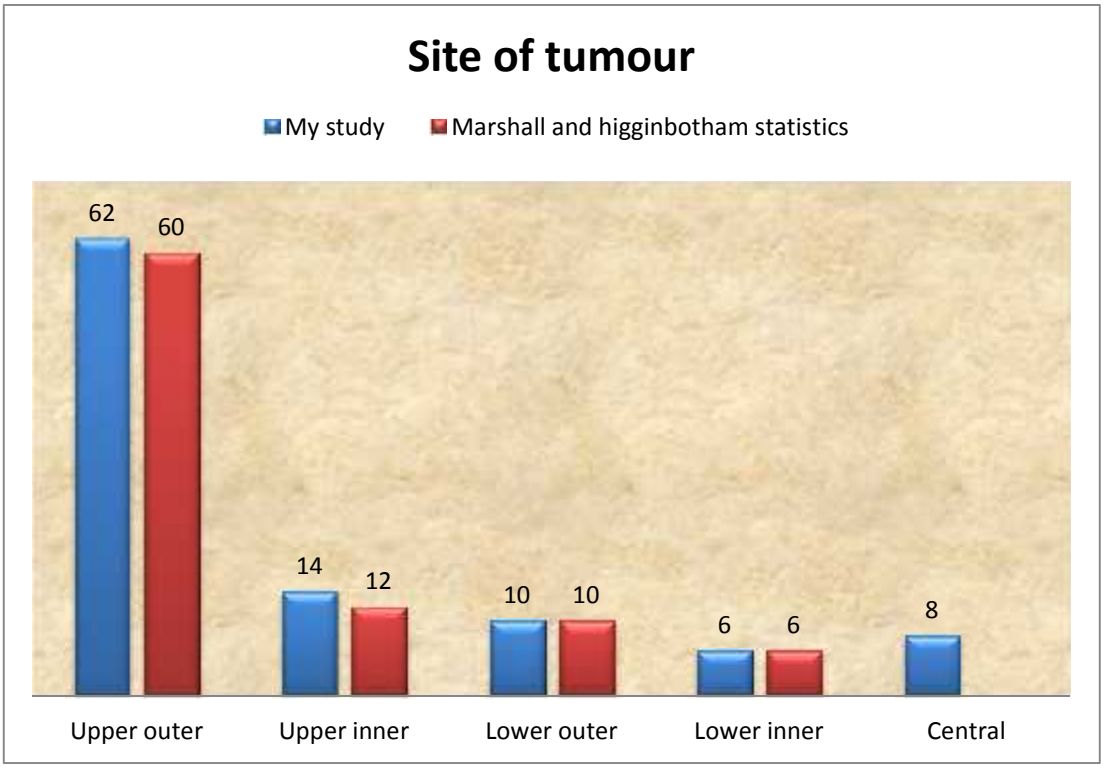
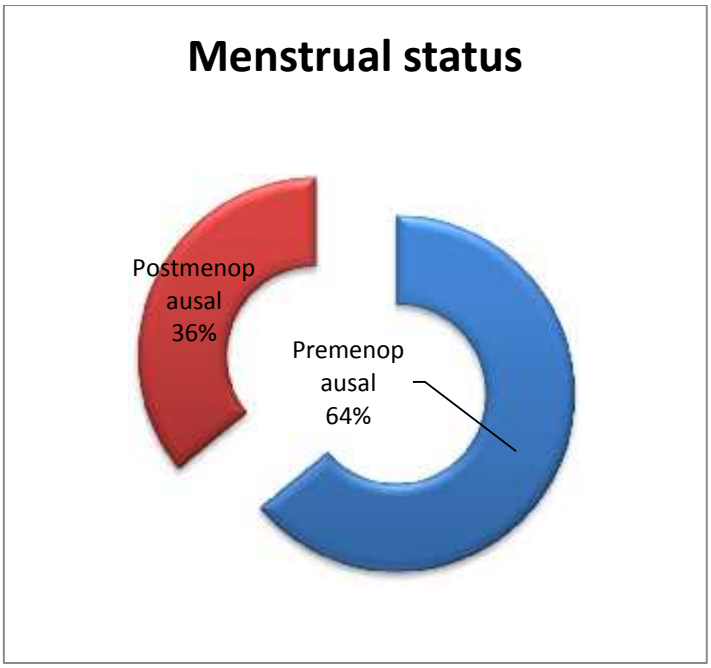


TABLE 5

MENSTRUAL STATUS

Menstrual status	No. of patients, n= 50	Percentage
Premenopausal	32	64
Postmenopausal	18	36

CHART 4



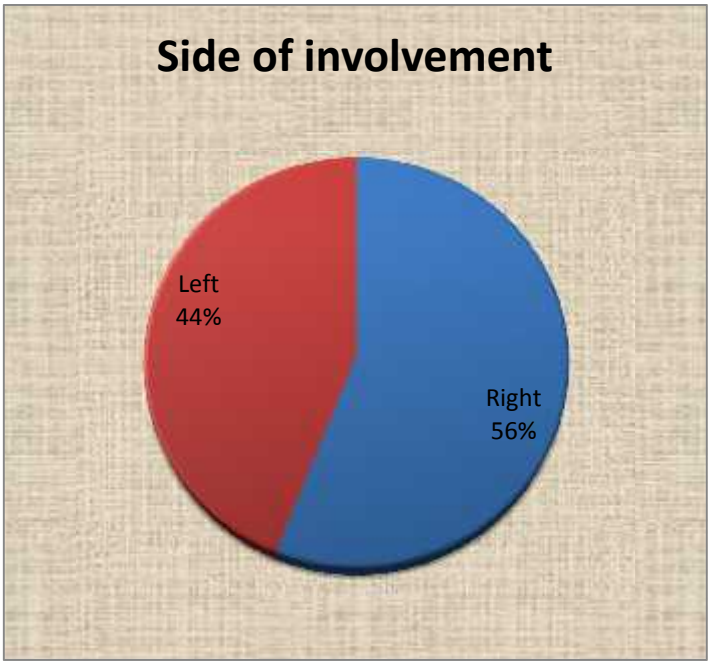
In my study 64% of patients were premenopausal and 35% were postmenopausal.

TABLE 6

SIDE OF INVOLVEMENT

Side involved	No. of patients, n=50	Percentage
Right	28	56
Left	22	44

CHART 5



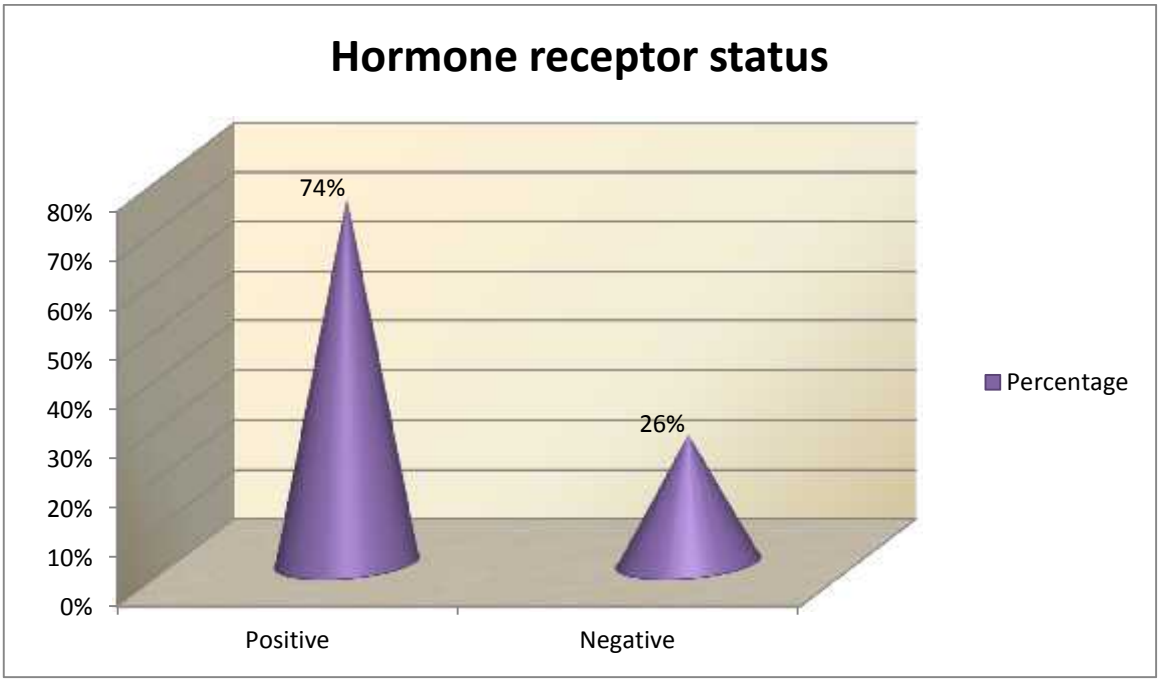
In my study right breast was involved in 56% of patients whereas left breast in 44%

TABLE 7

HORMONE RECEPTOR STATUS

Hormone receptor	No.of patients , n=50	Percentage
Positive	37	74 %
Negative	13	26%

CHART 6



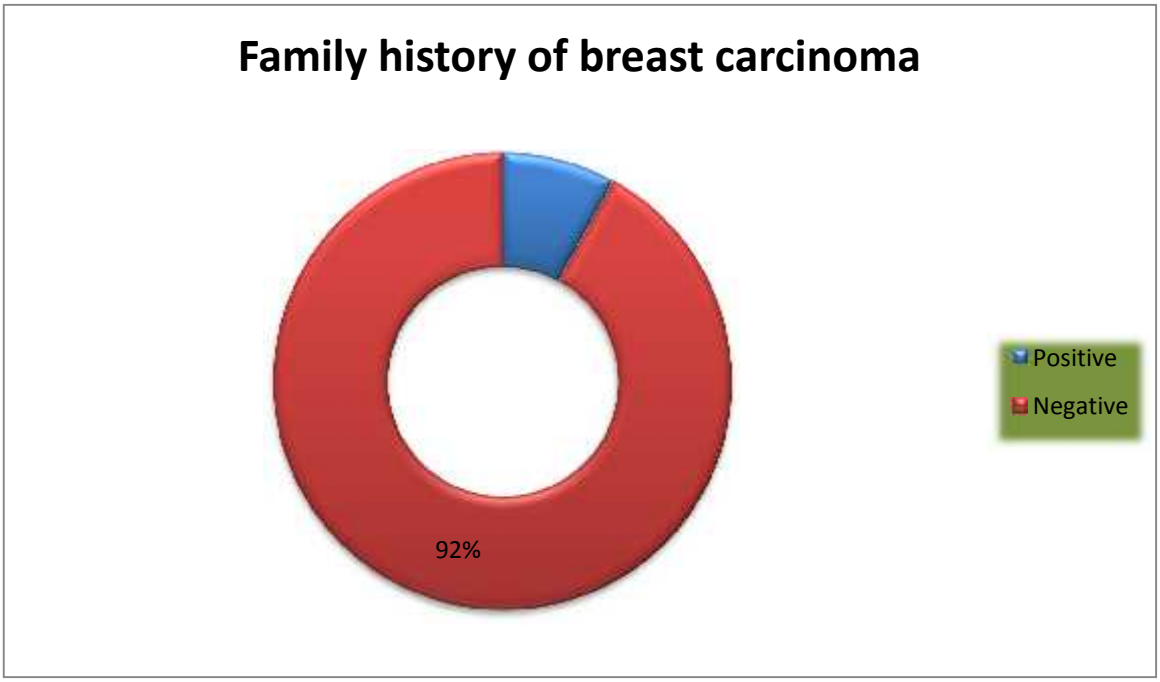
In my study 37 patients (74%) showed hormone receptor positivity and 13 patients (26%) showed hormone receptor negativity.

TABLE 8

FAMILY HISTORY

Family history	No. of patients , n=50	Percentage
Positive	4	8
Negative	46	92

CHART-7



In my study only 8% of patients had family history of breast cancer.

TABLE 9

DURATION OF TUMOUR

Duration of tumour	No. of cases, n=50	Percentage
< 2 months	17	34
>2-6 months	24	48
>6-12 months	7	14
>1 year	2	4

CHART 8

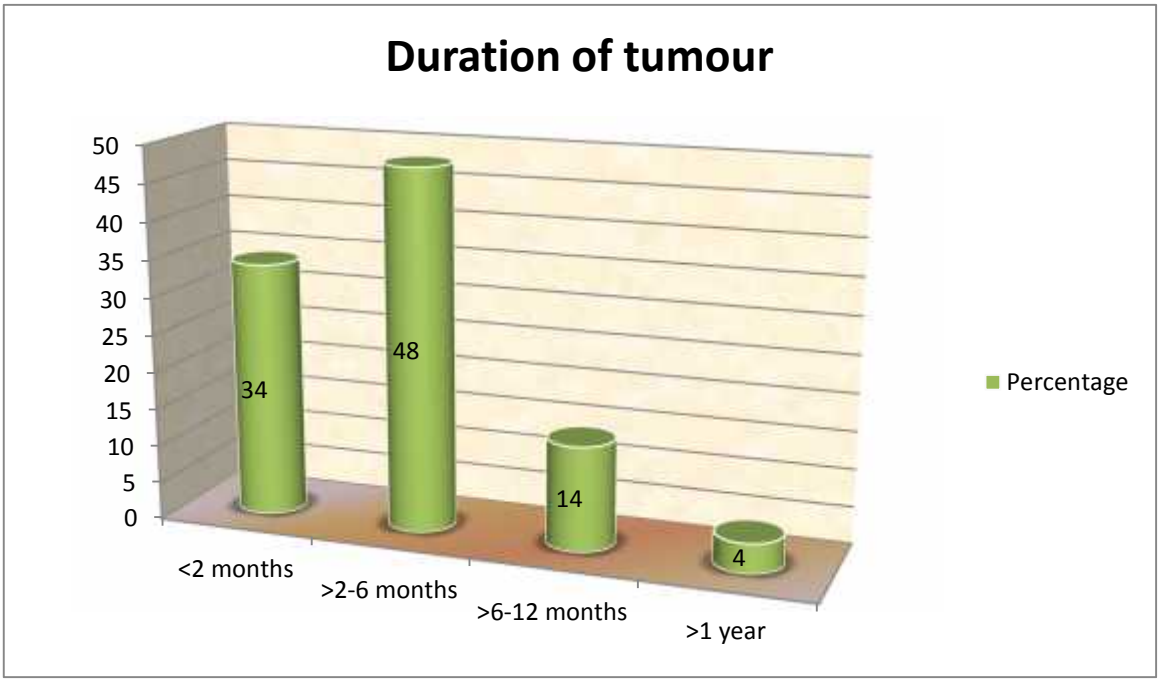
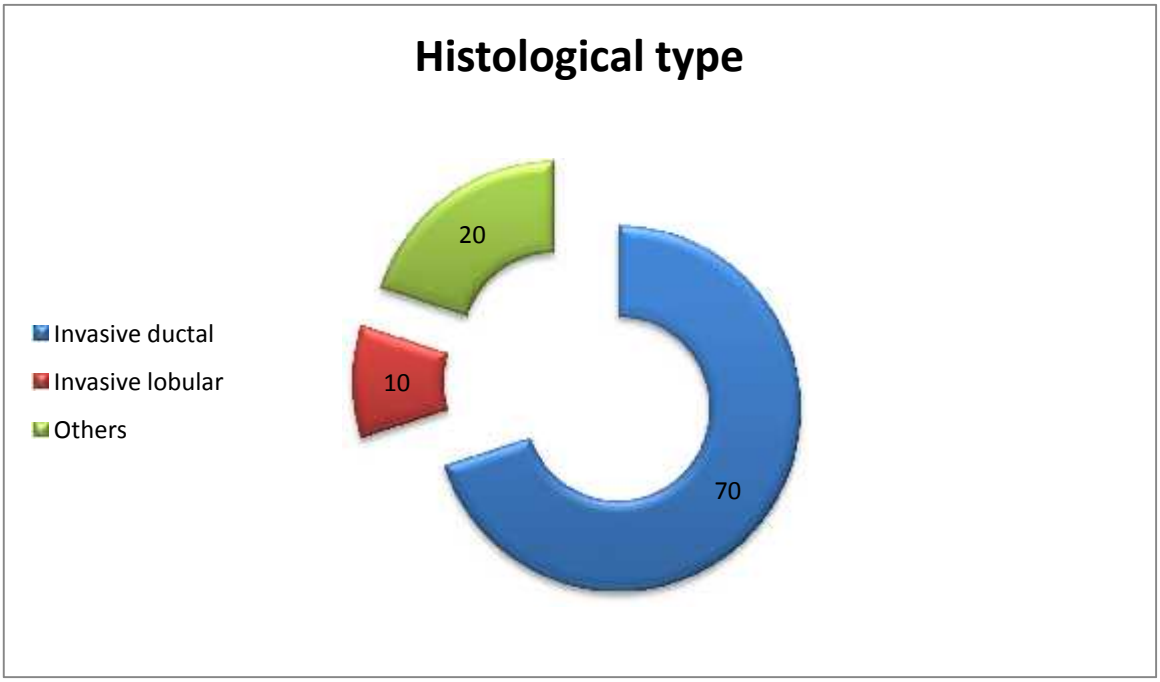


TABLE 10

HISTOLOGICAL TYPE

Histological type	No. of patients , n=50	Percentage
Invasive ductal carcinoma	35	70
Invasive lobular carcinoma	5	10
Others	10	20

CHART9



Invasive ductal carcinoma comprises 70% of patients in my study whereas invasive lobular is 10% suggesting that invasive ductal being the commonest type which is comparable with studies by saxena et al *

TABLE - 11

OPERABLE Vs INOPERABLE LABC

	No. of patients, n=50	Percentage
Operable LABC	16	32
Inoperable LABC	34	68

CHART 10

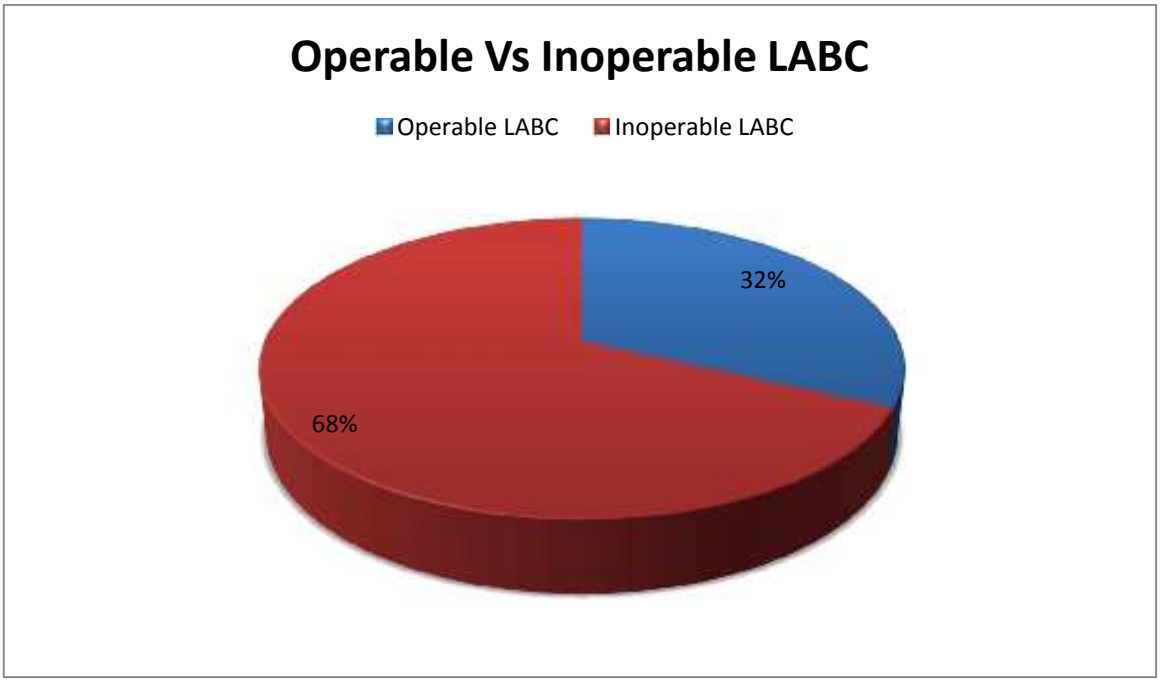


TABLE 12

OPERABILITY Vs HORMONE RECEPTOR STATUS

	Hormone receptor positive		Hormone receptor negative	
	No. of patients n=37	**Percentage**	**No. of patients, n=13**	**Percentage**
Operable LABC	13	35.1 %	3	23 %
Inoperable LABC	24	64.8 %	10	77 %

CLINICAL RESPONSE

In my study, clinical response occurred in 45 patients (90%) and stable disease in 5 cases (10%). Complete clinical response occurred in 13 patients (26%) and partial response in 32 patients (64%) .

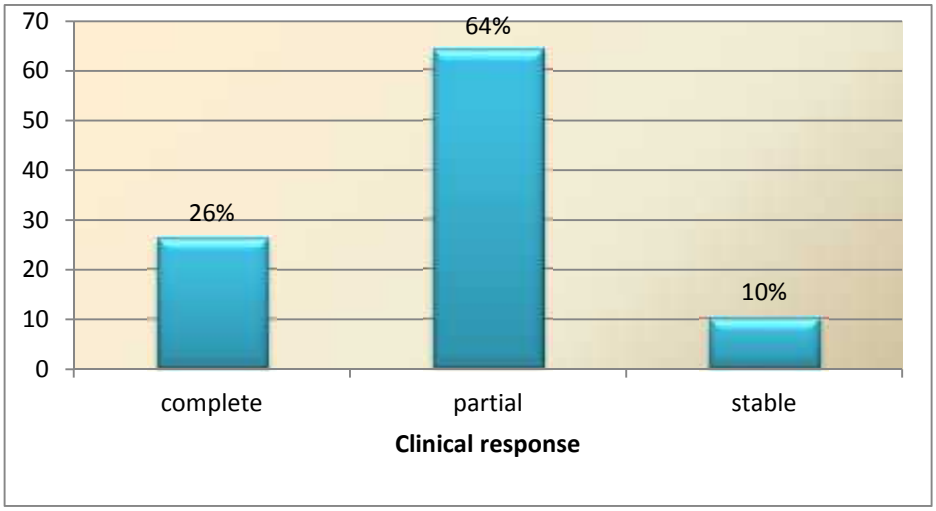
TABLE 13

CLINICAL RESPONSE

My study			Ochonma et al
Clinical response	**No. of patients, n=50**	**Percentage**	**Percentage**
Complete response	13	26%	12.9%
Partial response	32	64%	61.3%
Stable disease	5	10%	25.8%
Progressive disease	0	0	0

CHART 11

CLINICAL RESPONSE



In my study 33 (89.1%) patients with hormone receptor positivity showed a clinical response whereas 12 (92.3%) patients with hormone receptor negativity is showing the response.

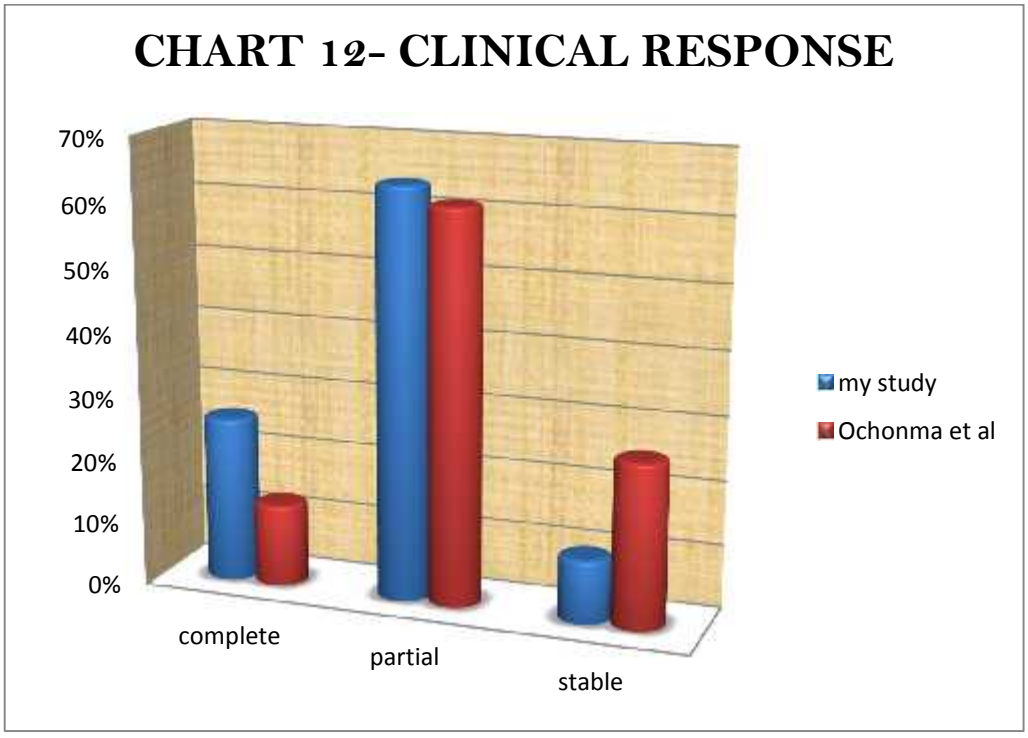


TABLE 14

CLINICAL RESPONSE Vs HORMONE RECEPTOR STATUS

Clinical response	Hormone receptor positive		Hormone receptor negative	
	No.of patients n=37	Percentage	No.of patients n=13	Percentage
Response +	33	89.1%	12	92.3%
Stable disease	4	10.8%	1	7.6%

CHART 13

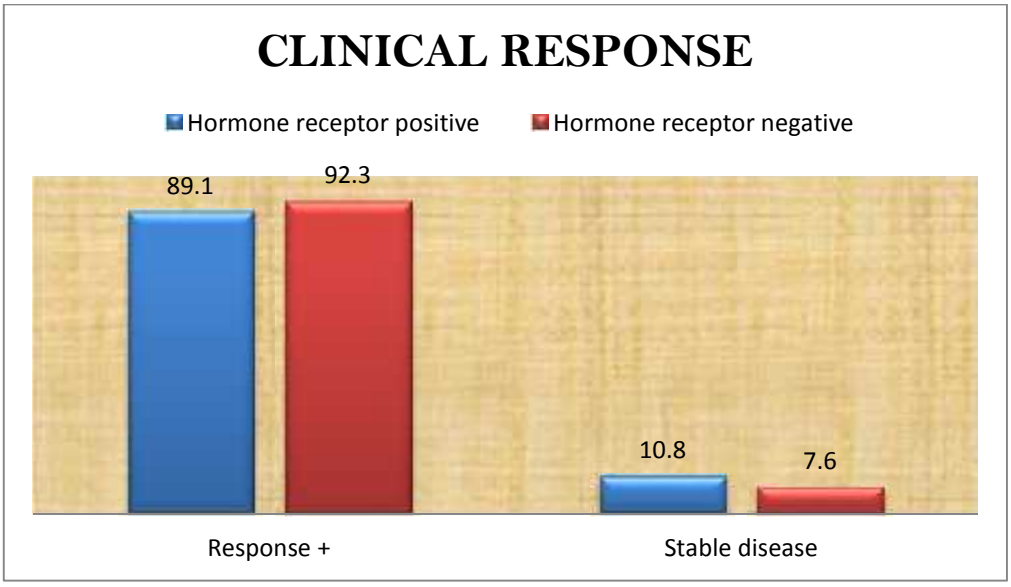


TABLE 15

CLINICAL RESPONSE Vs HORMONE RECEPTOR STATUS

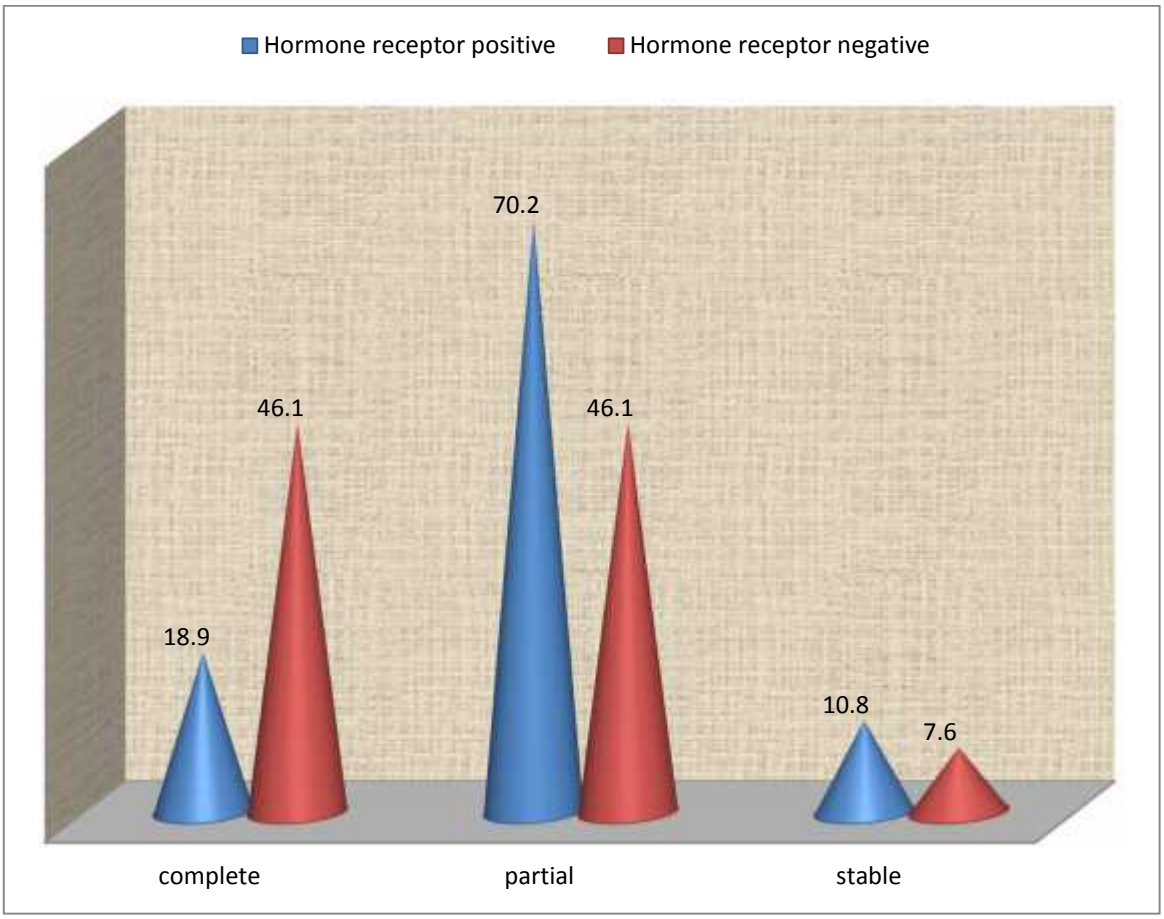
Clinical response	**Hormone receptor positive**		**Hormone receptor negative**	
	No. of patients n= 37	**percentage**	**No. of patients n= 13**	**Percentage**
Complete	7	18.9%	6	46.1%
Partial	26	70.2%	6	46.1%
Stable	4	10.8%	1	7.6%

The proportions of observations in different columns of the contingency table do not vary from row to row.

The two charecteristics that define the contingency table are not significantly related . P value = 0.156.

CHART 14

CLINICAL RESPONSE Vs HORMONE RECEPTOR STATUS



In my study complete response is showed by 46% of hormone receptor negative patients, partial response is higher in hormone receptor positive patients 70%.

Overall the response is higher in hormone receptor negative group.

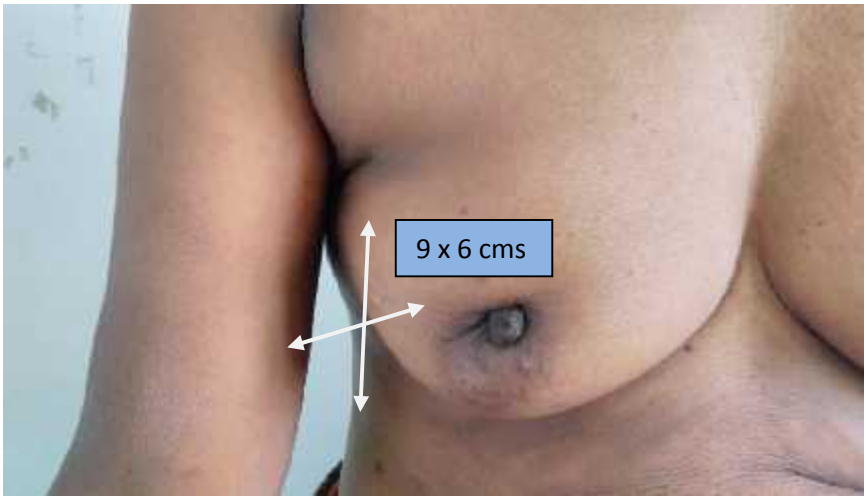


Fig 5- Clinical photograph – Before chemotherapy

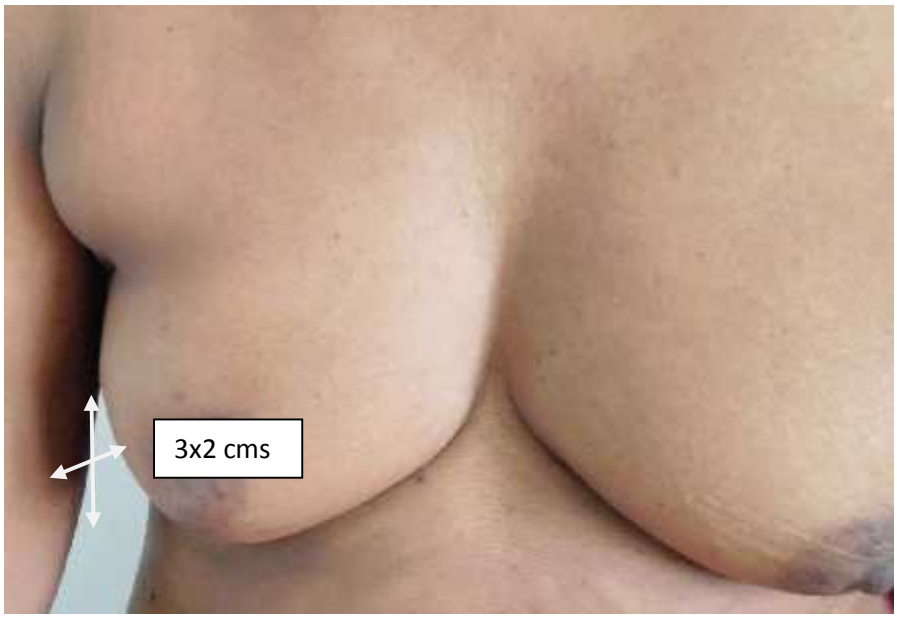


Fig 6 – Clinical photograph – After chemotherapy

CLINICAL RESPONSE

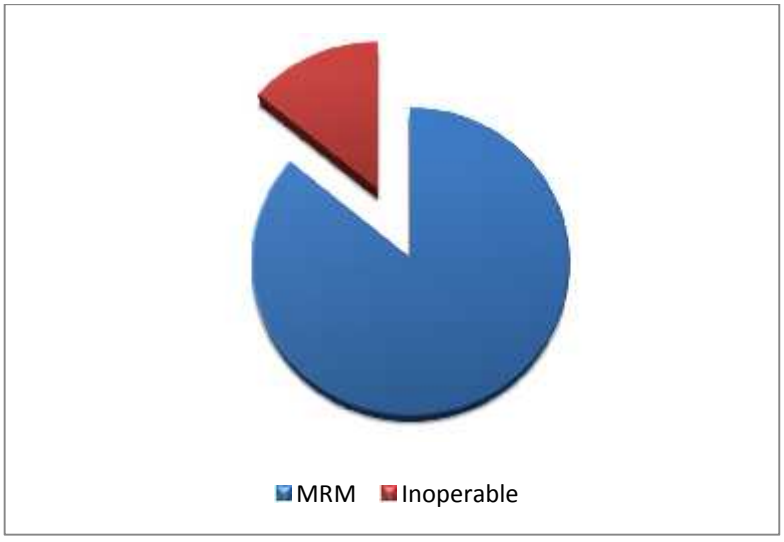
TABLE 16

SURGERY- MRM Vs INOPERABLE

Surgery	No.of patients	Percentage
MRM	43	86 %
Inoperable	7	14 %

CHART 15

SURGERY – MRM Vs INOPERABLE



86% of patients in my study underwent MRM whereas only 14% remained inoperable.

TABLE 17

SURGERY Vs HORMONE RECEPTOR STATUS

Surgery	Hormone receptor positive		Hormone receptor negative	
	No.of patients n=37	Percentage	No.of patients n=13	Percentage
MRM	30	81 %	13	100 %
Inoperable	7	19 %	0	0

In my study all hormone receptor negative patients underwent MRM. The characters in this table are significantly related , the P value = 0.02

CHART 16

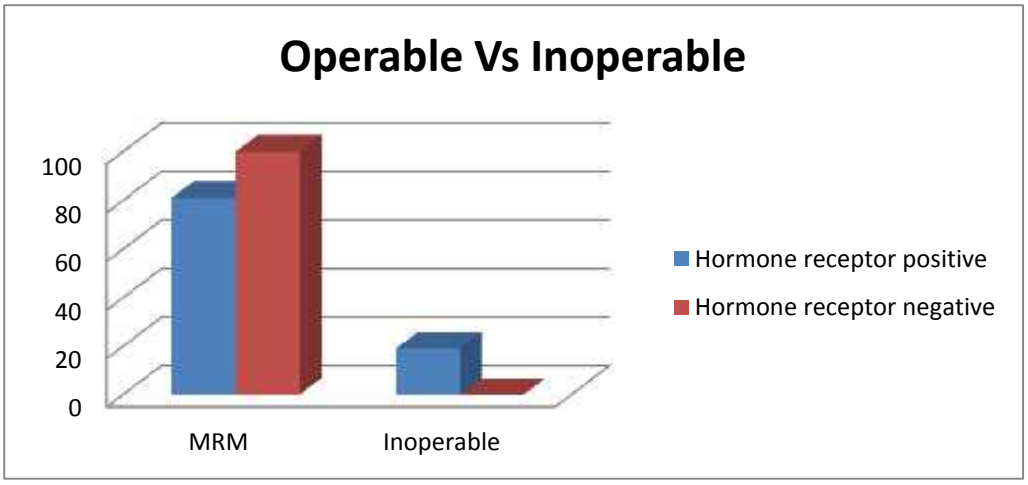


TABLE 18

PATHOLOGICAL RESPONSE

Pathological response	**No.of patients n= 43**	**Percentage**	**Trupti et al (Percentage)**
Complete response	9	21	14
Partial response	25	58	70
Residual disease	9	21	16

Pathological response occurred in 34 (79%) patients in my study, complete response is showed by 21% (9 patients), partial response by 25 patients (58%) and 9 patients (21%) showed residual disease.

CHART 17

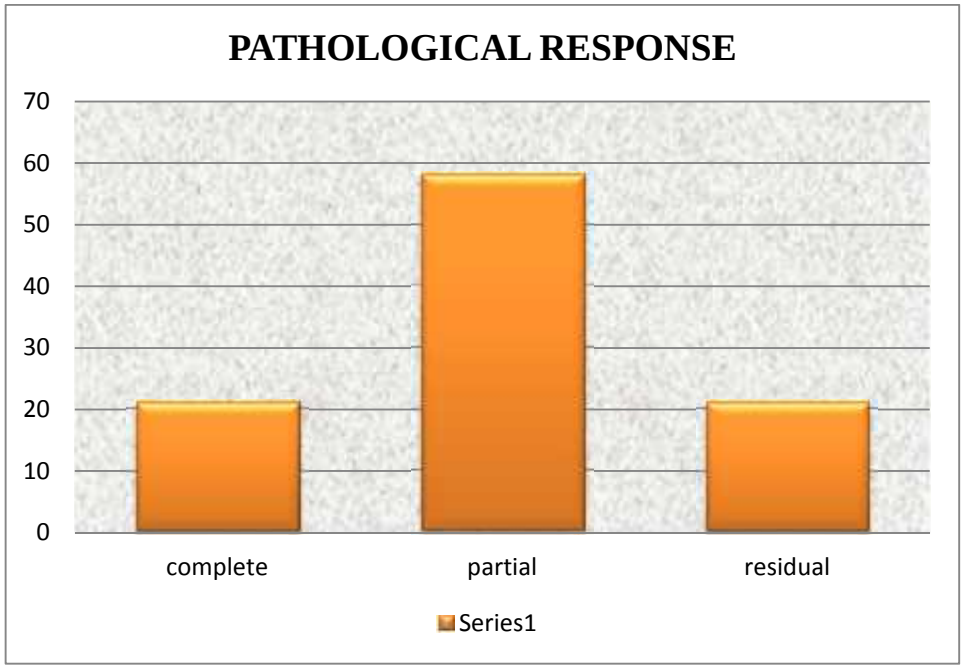


CHART 18 – PATHOLOGICAL RESPONSE

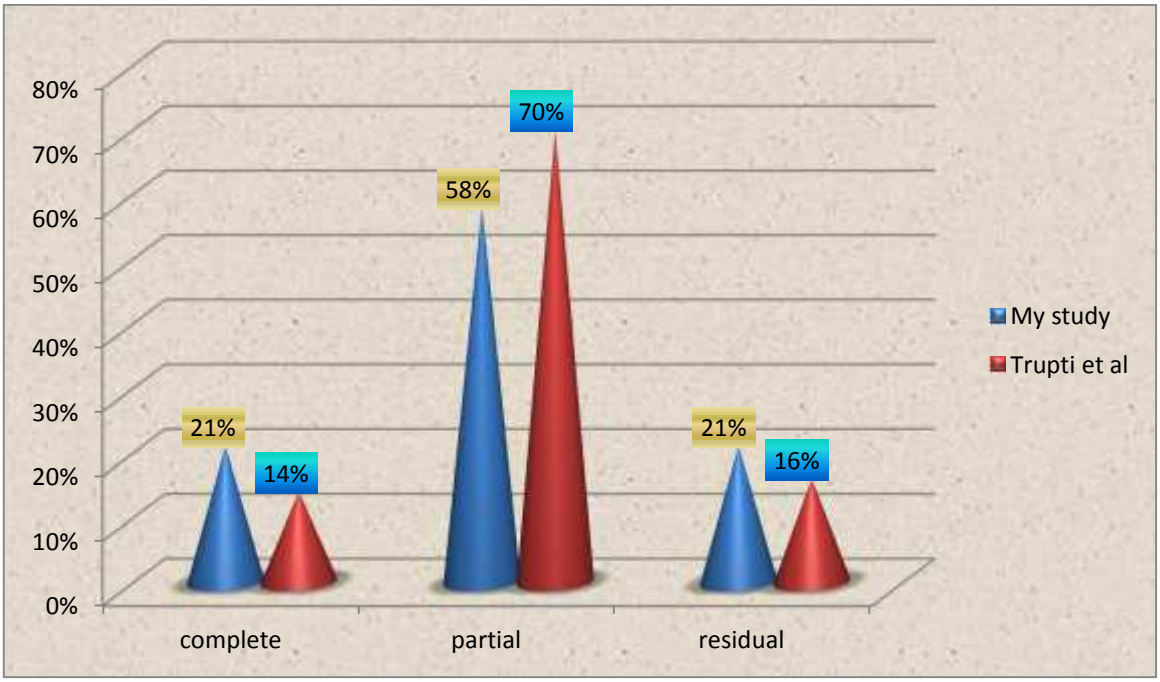
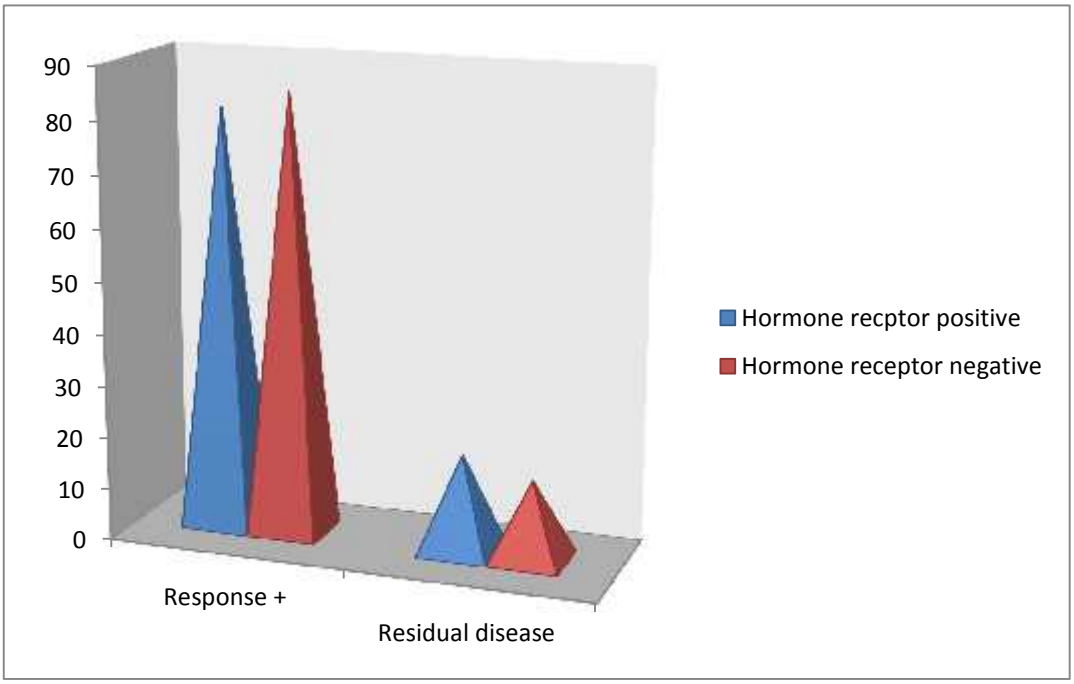


TABLE 19

PATHOLOGICAL RESPONSE Vs HORMONE RECEPTOR STATUS

Pathological response	Hormone receptor positive		Hormone receptor negative	
	No.of patients n=30	percentage	No.of patients n=13	Percentage
Response+	23	76.6%	11	84.6%
Residual disease	7	23.3%	2	15.3%

CHART 19



Pathological response occurred in 23 patients (76.6%) with hormone receptor positive status whereas it is 11 (84.6%) in hormone receptor negative group. Residual disease is found in 23.3% patients with hormone receptor positivity whereas it is 15.3% in hormone receptor negative group.

TABLE 20

PATHOLOGICAL RESPONSE Vs HORMONE RECEPTOR STATUS

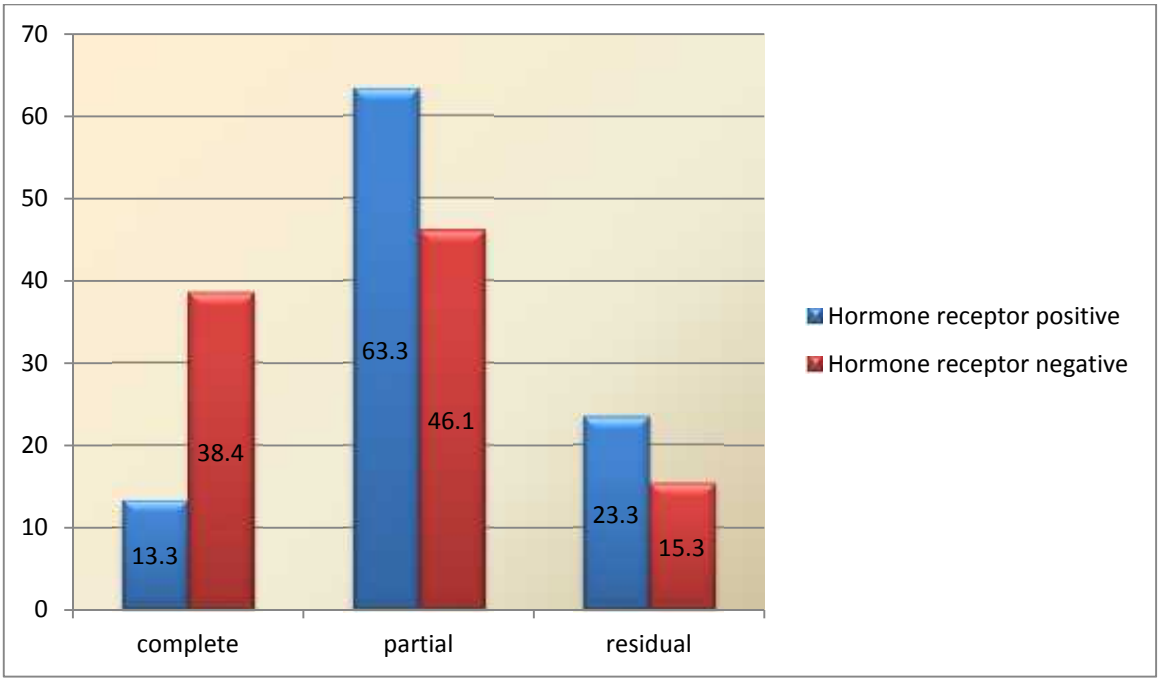
Pathological response	**Hormone receptor positive**		**Hormone receptor negative**	
	No.of patients n=30	**Percentage**	**No.of patients n=13**	**Percentage**
Complete	4	13.3%	5	38.4%
Partial	19	63.3%	6	46.1%
Residual disease	7	23.3%	2	15.3%

The proportions of observations in different columns of the contingency table do not vary from row to row

The two charecteristics that define the contingency table are not significantly related . (P value = 0.081)

CHART 20

PATHOLOGICAL RESPONSE Vs HORMONE RECEPTOR STATUS



Complete pathological response is seen in 38.4% patients with hormone receptor negativity and 13.3% with hormone receptor positive status. Partial response is more in hormone receptor positive group 63.3%.

Overall the response is higher in hormone receptor negative group

DISCUSSION

Locally advanced breast carcinoma comprises about 10 – 20 % of newly diagnosed breast cancer. [6] It refers to stage II B and stage III of carcinoma breast according to the TNM classification. It usually involves tumour size more than 5 cms or tumour fixed to chest wall or with skin ulceration, oedema of the skin or satellite nodules or regional lymph nodes but with no distant metastasis. Inflammatory breast cancer , classified as stage III B or III C in TNM staging , is a highly aggressive form of locally advanced breast carcinoma with metastatic potential.[33] High evidence of micro-metastasis and large volume of loco-regional disease will be present in this subset of patients.

The five- year survival rate in locally advanced breast carcinoma was 15% till 1940s. The results have remarkably improved with the better understanding of disease and team work among surgeon ,radiation oncologist and medical oncologist , with the accepted five- year survival rate of about 60%.

In earlier days, locally advanced breast carcinoma was thought to be a disease with no cure, but with the advancement of technology and knowledge , multidisciplinary management is accepted to be the treatment for LABC. In the first half of twentieth century, patients with locally advanced breast carcinoma underwent extensive radiotherapy and

aggressive surgical management. [33] William Halsted of John Hopkins university developed radical mastectomy for this patients. Haagensen and others , in 1940s revised the surgical indications in patients with LABC . Now the accepted strategy is neoadjuvant or systemic chemotherapy which is followed by loco-regional therapy either surgery or radiotherapy ,followed by adjuvant chemotherapy. Various large prospective trials have demonstrated the efficacy of neoadjuvant chemotherapy in locally advanced breast carcinoma. By the introduction of these multimodality treatment , the natural course of this disease has changed dramatically.[6]

Majority of the patients will respond to neoadjuvant / induction chemotherapy with anthracycline- based regimen , thus rendering large operable tumours to undergo breast conservation surgery and inoperable tumours to undergo resection. A large percentage of patients showed clinical and pathological response to anthracycline – based chemotherapy. The results are still better on addition of docetaxel or paclitaxel , used in combination with the anthracycline or as a separate regimen [34] . An objective response is achieved by more than 70% of patients , including complete pathological response of about 10- 25 %. [6] . Downstaging is experienced by many patients. Initially the patients are rendered disease free and long term control is achieved in about 70% of patients , with breast conservation possible in 10- 14% of patients . [6]In patients with clinically or radiographically positive axilla, mastectomy is accompanied

by nodal dissection of axilla. In node negative axilla, sentinel lymph node sampling is done followed by subsequent axillary dissection if the nodes are involved.

Fig 7- Clinical photograph of locally advanced breast carcinoma with nipple retraction

Fig 8- Peau d'orange appearance of skin

Fig : 9- Clinical photograph of locally advanced breast carcinoma with skin ulceration

HORMONE RECEPTOR STATUS

In my study 37 patients (74%) showed hormone receptor positivity and 13 patients (26%) showed hormone receptor negativity.

Patil et al, in 2011 [40] , conducted a study in which 77.5 % cases were hormone receptor positive whereas the hormone receptor negative cases being 19.9 %.

CLINICAL RESPONSE

In my study, out of the 50 cases of locally advanced breast carcinoma , clinical response occurred in 45 patients (90%) and stable

disease in 5 cases (10%). Complete clinical response occurred in 13 patients (26%) and partial response in 32 patients (64%) .

In a study by Sataloff et al [35] ,36 patients (86%) showed clinical response and stable disease in 5 patients (14%). 14 patients (39 %) showed complete clinical response , 17patients (47%) showed partial response.

Ochonma et al [37] , found that complete clinical response occurred in 12.9% patients whereas 61.3% patients had partial response and stable disease was observed in 25.8% of patients .

In my study , out of 37 patients who are hormone receptor positive, 7 patients (18.9%) had complete response, 26 (70.2%) had partial response and 4 patients (10.8%) had stable disease, whereas among 13 hormone receptor negative patients, 6 patients (46.1%) had complete response , 6 (46.1%) had partial response and 1 patient (7.6%) had stable disease.

SURGERY

In my study , 86 % of patients in my study underwent MRM whereas only 14 % (7 patiemts) remained inoperable after 3 cycles of chemotherapy. Out of the 43 patients (86%) who underwent MRM, 30 patients where hormone receptor positive whereas 13 were hormone receptor negative. Thus all hormone receptor negative patients underwent

MRM, whereas only 30 patients out of 37 (81%) of hormone receptor positive patients underwent MRM.

Schwartz et al, [38] study shows that 64% (103 patients) underwent MRM following neoadjuvant chemotherapy.

Fig:10- After modified radical mastectomy

PATHOLOGICAL RESPONSE

Out of 43 patients who underwent MRM, pathological response occurred in 34(79 %) patients in my study, complete response is showed by 21% (9 patients), partial response by 25 patients (58%) and 9 patients (21%) showed residual disease.

In the study by Trupti et al [36] , 7 patients (14%) had complete pathological response, 35 patients (70%) had partial response and residual disease was found in 8 patients (16%).

In my study , out of 30 patients who underwent MRM with hormone receptor positive status, 4 patients (13.3 %) had complete response, 19 (63.3%) had partial response and 7 patients (23.3%) had residual disease, whereas among 13 hormone receptor negative patients, 5 patients (38.4 %) had complete response , 6 (46.1%) had partial response and 2 patients (15.3 %) had residual disease.

CONCLUSION

Despite the rapid changes in all the fields in this era, from tissue surgery to nanotechnology level, every single lady is very much apprehensive about carcinoma breast and its fatal outcome. Even-though surgery can be offered to these patients, operations on the breast do still carry a social stigmata due to cosmetic loss ; it is a nightmare to the surgeon also regarding the fruit of extensive excision, post operative complications, blood loss and reconstructive surgeries.

In 1950s, the only procedure known was radical mastectomy. The mortality and morbidity associated with radical mastectomy led to the search for less extensive surgeries and the aids for achieving it. In the late 1970s,chemotherapy drugs were tried thus helping the surgeon to reduce extensive dissection. The history of breast carcinoma management significantly changed with the advent of neoadjuvant and adjuvant chemotherapy.

My study revealed clinical response in 45 patients (90%) and stable disease in 5 cases (10%) whereas pathological response in 34 patients (79%) and residual disease in 9 patients (21% cases) . Complete clinical response occurred in 13 patients (26%) and partial response in 32 patients (64%) . Complete pathological response is showed by 21% (9 patients) and partial response by 25 patients (58%).

In 1995, Sataloff et al reported 86% clinical response and 14% stable disease , complete clinical response and partial clinical response being 39% and 47% respectively. In 2013, Trupti et al, reported 14% complete pathological response, 70% partial pathological response and 16% stable disease.

In my study , out of 37 patients who are hormone receptor positive, 7 patients (18.9%) had complete clinical response, 26 (70.2%) had partial clinical response and 4 patients (10.8%) had stable disease, whereas among 13 hormone receptor negative patients, 6 patients (46.1%) had complete clinical response , 6 (46.1%) had partial clinical response and 1 patient (7.6%) had stable disease. Like wise, out of 30 patients who were hormone receptor positive (underwent MRM) , 4 patients (13.3 %) had complete pathological response, 19 (63.3%) had partial pathological response and 7 patients (23.3%) had residual disease, whereas among 13 hormone receptor negative patients, 5 patients (38.4 %) had complete pathological response , 6 (46.1%) had partial pathological response and 2 patients (15.3 %) had residual disease.

Statistical analysis of clinical and pathological response in locally advanced breast carcinoma between hormone receptor positive and hormone receptor negative patients proved the latter to be the better.

In my study, 86 % of patients underwent MRM whereas only 14 % remained inoperable. 100% of hormone receptor negative tumours were amenable for surgery , whereas only 81% hormone receptor positive tumours underwent MRM with 3 cycles of chemotherapy.

With these results, I would like to state that the response to neoadjuvant chemotherapy was significantly good in patients with negative hormone receptor status. Neoadjuvant chemotherapy renders surgery possible even in inoperable locally advanced breast carcinoma patients and the better results being seen in hormone receptor negative patients.

But it has to be emphasized that ,there are always more roads that are less travelled. Locally advanced breast carcinoma once thought to be incurable is offered the best possible management now with the help of neoadjuvant and adjuvant chemotherapy. Similarly, the knowledge of the role of hormone receptors in carcinoma breast gives us the every possibility to streamline the treatment guidelines. Likewise, many more advancements are yet to be discovered. The last line is yet to be written....

LIMITATIONS OF THE STUDY

- The study was conducted in tertiary care government setting and results may differ from those obtained from primary care setting or private sector.
- Sample size was small as only locally advanced breast carcinoma reported in my institution was included.
- Selection of chemotherapy was based on the common regimen available in my institution.
- Patients with operable locally advanced breast carcinoma accepted only modified radical mastectomy as surgical option.
- Further follow up could not be done as majority of people defaulted adjuvant treatment following surgery.

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ANNEXURE

PROFORMA

Name :

Age :

IP No :

Socioeconomic status :

Monthly income :

Educational Status :

Address :

Date of admission :

History of Present Illness

H/o lump in Rt/Lt breast :

1. Mode of onset
2. Duration
3. Rate of growth

H/o discharge from the nipple :

H/o pain :

H/o retraction of nipple :

H/o ulceration of skin over the swelling :

H/o loss of weight :

H/o loss of appetite :

H/o back pain :

H/o bony pain :

H/o OCP intake :

H/o Hormone replacement therapy :

Past History

H/o TB/Bronchial asthma/DM/HT/Thyroid disease/ epilepsy

Personal History

Marital status – Married/ Unmarried :

Menstrual History - Age of Menarche :

Regular/irregular cycles :

Pre/Postmenopausal :

Age of Menopause :

Obstetric History – Age at first child birth :

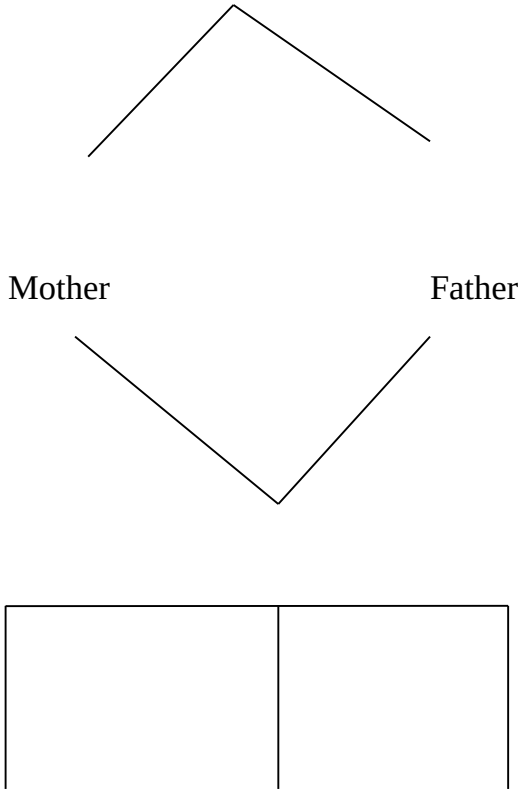
Last child birth :

Sterilised or not :

Lactational History

Family History

Family tree



PHYSICAL EXAMINATION

Local examination

Inspection:

Arms by the side, Arms raised above the head

1. Position

2. Size and shape of breast

3. Swelling

4. Ulcer

5. Skin over the breast
    a) Puckering
    b) Dimpling
    c) Ulcer
    d) Nodule
    e) Peau d orange
    f) Engorged veins

6. Nipple – Position

   Size and shape

   Retraction

   Discharge

7. Areola

8. Arm & Thorax – nodules/ oedema

9. Axilla & supraclavicular fossa

PALPATION

1. Local rise in temperature and tenderness
2. Situation
3. Number
4. Size and shape
5. Surface
6. Margin
7. Consistency
8. Fixity to skin
9. Fixity to breast tissue

10. Fixity to underlying fascia and muscles
11. Fixity to chest wall
12. Palpation of nipple
13. Ulcer

EXAMINATION OF LYMPH NODES

1. Axillary lymph nodes
2. Supraclavicular lymph nodes

Opposite Breast :

Axilla :

GENERAL EXAMINATION

CVS :

Abdomen :

Bones :

Per rectal examination :

Per vaginal examination :

STAGING T N M **Stage** :

INVESTIGATIONS

1. Blood TC

   DC

   Hb %

2. Blood- urea

   Sugar

   Creatinine

3. LFT
4. Chest Xray – PA view
5. ECG
6. Blood Grouping & Typing
7. Biopsy
8. FNAC
9. CT chest/ CT abdomen
10. X-ray DL/LS spine – AP & lateral views

Staging of the disease :

ER/PR status :

Neoadjuvant chemotherapy regimen :

No.of cycles :

RESPONSE

Size :

Fixity to skin :

Fixity to chest wall :

Axillary lymph nodes :

Surgery - MRM/BCS :

Findings :

HPE report :

DATA KEY

Age group	
< or = 40	1
41-50	2
51 - 60	3
> 60	4

Side	
Right	1
Left	2

Site of tumour	
Upper outer quadrant	1
Upper inner quadrant	2
Lower outer quadrant	3
Lower inner quadrant	4
Central	5

Menstrual Status	
Premenopausal	1
Postmenopausal	2

Duration of tumor	
< 2 months	1
2 -6 months	2
>6 - 12 months	3
> 1 year - 2 yr	4
> 2 years	5

Family history	
yes	1
no	2

Histological type	
ILC	1
IDC	2
Others	3

T stage	
T2	1
T3	2
T4	3

Tumour size	
< 2 cm	1
2 - 4 cm	2
> 4 - 6 cm	3
> 6- 8 cm	4
> 8 - 10 cm	5
> 10 cm	6

N stage	
N0	1
N1	2
N2	3
N3	4

Tumour stage	
II B	1
III A	2
III B	3
III C	4

Estrogen receptor (ER)	
positive	1
negative	2

Progesterone receptor (PR)	
positive	1
negative	2

Clinical response (CR)	
complete	1
partial	2
stable	3
progressive	4

Pathological response (PR)	
complete	1
partial	2
residual	3

நோயாளிகளுக்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்
(மருத்துவ ஆய்வில் பங்கேற்பத்திற்கு)

ஆய்வு செய்யப்படும் தலைப்பு:
பங்கு பெறுவரின் பெயர்:
பங்கு பெறுவரின் வயது:

		பங்கு பெறுவர் இதனை ✓ குறிக்கவும்
	நான் மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்களை படித்து புரிந்து கொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன்.	☐
	நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.	☐
	இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்காள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.	☐
	இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.	☐
	இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன் எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின் படி நடந்து கொள்வதுடன், ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ, அல்லது எதிர்பாராத, வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்றேன்.	☐

பங்கேற்பவரின் கையொப்பம் / ..... இடம் .....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் /..... இடம் .....

ஆய்வாளரின் பெயர் .....

மையம் .....

கல்வியறிவு இல்லாதவற்கு (கைரேகை வைத்தவர்களுக்கு) இது அவசியம் தேவை

சாட்சியின் கையொப்பம் /..... இடம் .....

பெயர் மற்றும் விலாசம் ....

MASTER CHART

Name	Age	Menstrual status	Parity	family h/o	Side	Quadrant	duration of tumour	Size	T stage	N stage	tumour Stage	ER status	PR status	histological type	Surgery	Clinical response	Parhological response
Amrithalakshmi	2	2	1	2	2	1	2	3	3	2	3	2	2	1	1	1	1
Anandhi	2	1	2	2	1	1	3	6	3	2	3	2	2	1	2	1	1
Anitha	2	1	2	2	1	1	1	4	2	2	2	1	1	1	2	2	2
Anitha	2	1	2	2	2	3	1	5	2	3	2	1	1	3	2	2	3
Ayyammal	2	1	2	2	2	1	2	6	3	4	4	1	1	2	2	2	2
Chellamani	3	2	2	2	1	1	1	4	2	2	2	1	1	1	2	2	2
Chellammal	3	2	1	2	1	3	3	6	3	2	3	1	1	2	2	2	3
Chellatahi	2	1	1	2	1	1	1	3	2	2	2	1	1	1	2	1	2
Chidambarammal	2	1	2	2	2	1	2	4	2	3	2	2	1	1	2	2	2
Chindu	4	2	2	1	2	5	1	4	3	3	3	2	2	1	1	1	1
Esakkiammal	1	1	1	2	1	4	1	3	2	2	2	2	2	3	2	3	3
Esakkithai	3	2	2	2	1	1	3	4	2	2	2	1	1	1	2	2	2
Gnanapackiyam	3	2	1	2	2	1	1	3	2	2	2	1	1	1	2	2	2
Gnanasundari	3	2	5	1	2	3	3	4	2	2	2	1	1	3	2	2	2
Gurulakshmi	2	1	2	2	1	3	1	3	3	2	3	1	1	1	1	1	1
Indira	2	1	3	2	1	2	2	4	2	2	2	2	1	1	2	2	2
Iyyammal	2	1	2	2	1	1	2	3	3	2	3	1	2	1	2	3	3
Karpagavalli	3	2	2	2	2	1	2	4	2	2	2	2	1	1	2	2	3
Karuppayammal	2	1	1	2	1	1	1	4	3	2	3	1	2	1	2	2	2
Lakshmi	3	2	4	2	1	1	2	3	3	2	3	2	2	1	2	2	2
Lakshmi	3	2	0	2	1	2	4	6	3	1	3	1	1	3	2	2	2
Lakshmi	3	1	2	2	1	5	2	3	3	2	3	1	2	1	2	1	2
Lakshmi	3	1	2	2	2	4	3	4	2	2	2	1	1	1	2	2	2
Leelavathi	2	1	2	2	1	1	2	4	3	2	3	1	1	1	2	2	2
Mahalakshmi	1	1	2	2	1	1	2	5	3	2	3	1	2	3	2	3	3
Mallika	3	2	0	2	2	1	3	6	3	2	3	1	1	2	2	2	2
Mallika	1	1	2	2	1	1	2	3	2	2	2	1	1	1	2	1	1
Manorama	3	2	1	2	1	4	2	5	2	3	2	1	1	3	2	2	2
Mariammal	2	1	1	2	1	1	2	5	3	2	3	1	1	1	2	1	1
Muthammal	3	2	3	2	2	1	2	5	3	2	3	2	1	1	2	1	2
Muthammal	1	1	1	2	1	1	1	4	3	2	3	2	2	1	1	1	1
Muthulakshmi	1	1	2	2	2	3	2	3	3	2	3	2	2	1	2	2	3
Mydeenbbeevi	1	1	2	1	2	5	2	5	3	2	3	1	2	3	2	2	2
Nazheer Beegum	3	2	2	2	1	1	1	4	3	2	3	1	1	1	2	2	2

Nellaivathi	3	2	3	2	1	2	3	3	3	2	3	1	1	1	2	2	2
Packiyalakshmi	2	1	3	2	1	1	1	4	2	3	2	1	1	3	2	3	3
Pakkiyathai	2	2	2	2	1	1	1	5	3	2	3	1	1	3	2	2	2
Paripoornam	2	1	1	1	2	1	2	4	2	2	2	2	2	1	2	2	2
Ramalakshmi	3	2	2	2	1	1	2	5	2	3	2	1	1	3	2	2	2
Santhi	2	1	1	2	2	2	1	5	2	2	2	2	1	1	2	1	1
Saraswathi	3	2	3	2	2	1	2	3	3	2	3	2	2	1	2	1	1
Saraswathy	2	1	3	2	2	2	1	3	3	2	3	1	1	1	2	3	3
Saroja	2	1	2	2	2	1	2	3	2	2	2	2	2	2	2	2	2
Selvapakkiyam	2	1	1	2	2	1	4	4	2	2	2	1	1	1	2	2	2
Selvi	1	1	1	2	1	1	1	4	1	2	2	2	1	1	2	2	2
Selvi	1	1	2	2	2	1	2	4	3	2	3	2	2	2	2	1	2
Selvi	1	1	1	2	2	1	1	4	2	2	2	1	1	1	2	2	2
Shanthi	2	1	2	2	2	2	2	3	3	3	3	2	1	1	2	2	2
Sivakumari	2	1	1	2	1	2	2	6	3	2	3	2	2	1	2	2	2
velithai	1	1	0	2	1	5	2	4	3	3	3	1	2	1	2	2	2